FDA CTP - Third Party Governance of Industry-Sponsored Tobacco Product Research: A Public Workshop

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A Matter of Record
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FOOD AND DRUG ADMINISTRATION
CENTER FOR TOBACCO PRODUCTS

THIRD PARTY GOVERNANCE OF INDUSTRY-SPONSORED TOBACCO PRODUCTS RESEARCH: A PUBLIC WORKSHOP

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This transcript has not been edited or corrected, but appears as received from the commercial transcribing service.

C O N T E N T S

P R O C E E D I N G S
(8:30 a.m.)
Welcome and Overview
Introduction of Workshop Moderator

DR. ASHLEY: Good morning. If you guys could take your seats, that would be great.

Welcome to the first day of FDA's public workshop on Third-Party Governance of Industry-Sponsored Tobacco Product Research. My name is David Ashley. I'm the director of the Office of Science here at CTP, and it is my honor and privilege to introduce Mitch Zeller, CTP's new center director, who will be delivering our welcoming remarks.

DR. ZELLER: David knows I'm not a doctor, and I don't play one on TV, either.

Let me start by welcoming everyone to this public workshop on Third-Party Governance of Industry-Sponsored Tobacco Product Research. And I want to sincerely thank everyone for their participation in today's and tomorrow's proceedings.

This is an issue near and dear to my heart. I've worked on it for the past 10 years, going back to the first public session a group of us held on the topic following the SRNT meeting in New Orleans in 2003. And just for the record, that was a public meeting, and it included participation from the tobacco control and research communities as well as the tobacco industry.

Since then, many of us in this room have had smaller gatherings to explore governance issues and examine funding and governance models from non-tobacco sectors. I've also worked with some of you here on a publication that articulated a set of criteria to evaluate potential funding models, and then applied those criteria to several models to see how the models and the criteria held up. And that paper appeared in tobacco control back in 2009.

There is no escaping the fact that this is a contentious issue between various sectors, from tobacco control and public health groups to the tobacco industry. It's contentious in part because

Page 5

there remains significant trust issues for many in tobacco control and public health, given the historical behavior of the tobacco industry.

This workshop is not designed to address or resolve those trust issues, but those trust issues exist, and we all have to be aware of them when we're gathering to talk about the most appropriate governance structure for tobacco product research, especially research to be conducted by tobacco companies.

A lot has been said about the word "stakeholder" in the context of CTP's regulatory responsibilities broadly, and especially as regards the topic of this workshop. And I understand the sensitivities here.

For me, the key part of the word stakeholder is stake. Many different parties and sectors of society have a stake in whatever governance structure is established. That structure will guide the research needed to create the regulatory science base upon which CTP will make policy, craft guidance and regulations, and evaluate sponsors'

Page 6

applications. And the reality is that it will be the tobacco companies who will be submitting applications under Section 911 of the Tobacco Control Act for MRTP orders. The law provides for that regulatory pathway, and the sponsors are entitled to know the rules of the road.

But the issues embedded in Section 911 are complex. Given the history of the marketing of products bearing descriptors such as light and low-tar, Congress made clear that Section 911 had multiple purposes. Yes, it is the pathway for FDA to issue MRTP orders based on a sufficient science base. And we're here today and tomorrow to explore governance structures in that context. But Section 911 is also the provision designed to keep potentially misleading MRTP claims off of the market. The Center has the responsibility to hear from all interested parties on the governance issues, and this workshop is the first step in that process.

The workshop is really important. It represents a key opportunity for all of you to

Page 7

share your insights and perspectives, and just as important, it's an opportunity for CTP to listen and to learn. And as much as I'd like to, I'm not going to be able to stay for today's and tomorrow's sessions, but I will follow it with great interest in the days and weeks to come.

With that, I want to wish you all the best of luck for what I am certain will be a productive, provocative, and stimulating two days. Thank you all. Have a great meeting, and let me turn it back to David.

(Applause.)

DR. ASHLEY: Again, welcome to everyone. Glad you are here. Our hope is that this workshop will be a step forward in addressing CTP's need for reliable, accurate, dependable data upon which we must rely to make regulatory decisions.

Family Smoking Prevention and Tobacco Control Act required FDA to consult with the Institute of Medicine on the development of regulations or guidance on the scientific evidence required for assessment and ongoing review of

Page 8

modified-risk tobacco products. Specifically, Section 911 of the Act states, "The regulations or guidance issued under paragraph 1 shall be developed in consultation with the Institute of Medicine and with the input of other appropriate scientific and medical experts on the design and conduct of such studies and surveillance."

Now, the Institute of Medicine published their report, titled Scientific Standards for the Studies on Modified-Risk Tobacco Products, in December of 2011. The purpose of this public workshop is to discuss Recommendation 10 in the IOM report regarding the governance of studies, which states that, "MRTP sponsors should consider use of independent third parties to undertake one or more key functions, including the design and conduct of research, the oversight of specific studies, and the distribution of sponsor funds for research. Such independent third parties should be approved by the FDA in advance of the research."

Now, we have invited interested parties, including regulated industry, with a range of

Page 9

different perspectives on this issue to describe their experiences and offer their views of third-party governance.

The purpose of the workshop is to provide an opportunity in a public forum for FDA to hear from those with experience and an informed view on this issue. Therefore, several FDA representatives are in attendance and we listen closely to the perspectives described over the next two days. We'll also be opening a public docket soon on this topic, which will provide an opportunity for additional comment from interested parties to be entered into the public record.

The workshop and the opening of the public docket for comment are just the initial steps that FDA is taking as we begin to explore the concept of third-party governance and learn about some of the governance models that have been or are being used in other sectors.

The workshop will be moderated by Abby Dilley from RESOLVE, and I'll now turn the microphone over to her. Thanks, Abby.

Page 10

Workshop Moderator – Abby Dilley

MS. DILLEY: Good morning. So as David said, my name is Abby Dilley, and the organization I work for is named RESOLVE. It may be an unfortunate name, given what Mitch said. We're not resolving issues today. It is for primarily information gathering from diverse perspectives. And my role will be as a moderator, and in that capacity to help support -- along with Beth Weaver, my colleague, and others at CTP, some staff from CTP, to hopefully support a good couple-a-day meetings to achieve that particular goal, which is to gather information.

We're doing that in a variety of ways. We'll have presentations from a variety of invited speakers both today and tomorrow. And then we'll also have question and answer sessions, some immediately after the presenters give their remarks so we have questions for clarification; and then we also, as you see over the course of the agenda for the day and a half -- that there is opportunity for longer stretches of Q&A; and then also a public

Page 11

comment period tomorrow, where people have preregistered per the notice about this meeting to speak during that period.

We also have people not only participating in the room, but also virtually. There is a webcast going now. There's an e-mail address. For those of you who are listening remotely, the way to access that e-mail to send a question is through just a click right on the website.

So if you've gotten into the meeting, then you're on the website. You just need to click on that. So we'll be, at periods of time, taking some of those questions that we're receiving remotely to try and, again, expand the opportunity to gather information and from different people participating, both in person and remotely.

Part of helping support a meeting is to keep the meeting on time, on task, and on track. So hopefully, we'll be able to do that, and then also establish some meeting protocols to help support the meeting.

I have worked on tobacco control and

Page 12

regulation issues for a while, but I don't pretend to be an expert on this particular issue. Some of my questions that I may ask in follow-up might reflect that limited expertise, but hopefully they won't be too out there.

I will read a question submitted either via e-mail or we have cards over on the table over there, if people would prefer to submit questions via card. There are cards there. You can just put them in the basket, and over lunch break, for example, we can gather some more information and questions from the website, the e-mail address, and also cards. And there may be need for follow-up to make sure that I express the question correctly.

So I just want to give people a sense of how we're gathering information and have an opportunity to put in some questions to the panel members.

I just wanted to walk through the agenda. Hopefully, when you came in and got your name tag, you also received some materials, including the agenda for today, and that looks like this with that on there. And there are two stapled pieces

Page 13

that are the slides, the speakers. I think they're today and tomorrow. No, just today. Sorry, just today. And then there is a feedback form in blue. And when you have a chance to fill that out, there's a place over here on the table, again, for those forms.

So I just wanted you to know that those materials are there. If you haven't gotten them, they're out at the front desk where you walked in to get your name tag.

If you look at the agenda, there are basically five primary sections on the agenda. There's first an overview of the IOM report, and MRTPs, and governance structures. And Daniel Carpenter is here to give that overview. We'll then take some questions and answers after his presentation.

Then we have a panel that will go over -- through a break as well, a panel of public health experts, some of whom have written articles on this topic as well as researchers and the academic and other communities conducting research

Page 14

in this area or relevant areas.

As you can see from the overview of the agenda, the Q&A period for that session will be after lunch. And just on that note, we're taking an hour break for lunch. And outside, you'll see a book -- if you're not familiar with this area, there's a book of suggestions for nearby areas so you can have lunch and be back here in time for the start-up of the Q&A session for that first panel.

Then the third section is a panel of experts with experience developing and are involved with third-party governance models. Just a note on that, in the IOM report -- and I'm sure Daniel will speak to this, some of the models suggested in there. This is to have a couple other models to throw into the mix for consideration and think through in terms of how they approached third-party governance structures. And then there will be an opportunity for additional Q&A after that.

Then tomorrow morning, we will start with a public comment period. That's really the fourth section in the agenda, if you will, tomorrow, at

Page 15

the beginning of the day.

Then the last section of the meeting will be a panel of representatives from companies, tobacco manufacturers, and other products, as well as research and policy consultants, some of whom have developed ideas around third-party governance structures.

So that's the five sections, if you will, of the overall agenda.

Now, for the format for presentations and Q&A, each speaker has been given some time, about 10, 15, in some circumstances, like our first presenter, 20 minutes to give comments. And then we'll have an opportunity -- there will be some lights up here to give you the sign of, you're getting close to the end of your time, and then red. Just try and keep relatively within the time limits.

Then we'll have some opportunity to ask some follow-up questions for clarification. We'd really like to keep those as much as possible to clarification questions from the presentation, so

Page 16

we're extracting as much information out of those, and then keep more of the substantive questions for the panels to the Q&A.

Obviously, that's hard to distinguish very discretely between those two, but mostly, it's to make sure we stay on time and then can get to the longer Q&A period with more detailed questions.

We will have people who have microphones. This is being recorded, so there's a transcript that will ultimately be available from the CTP website. So we want to use the microphones, both so people can hear the question -- it's a big room; you can hear fairly well now, but I'm also on a mic -- so everybody can hear the question and keep things moving along as well as being able to be part of the transcript.

If you would, introduce yourself. We're not going to go around the room and have everybody introduce themselves, but if you could do that in asking a question, that would be great. If you fill out a card or people are sending a question by internet, you don't need to identify yourself.

Page 17

We're not going to necessarily list those, but just take questions as we go. But I think, just in the room, it's helpful, a little bit helpful.

Then at the conclusion of each panel, those sections, except for the public comment period because we don't have Q&A associated with public comment, there will be the opportunity, at least, I think, for almost every session, at least an hour for questions for the panel members. So there will be opportunity to do that.

Again, sometimes it will be from holding up hands. Sometimes, it will be from taking questions off the e-mails and from the basket over there, where you can put some index-card questions. And we may not get to every question.

We'll try and get to as many as we can within the allotted time. We really don't want to run off schedule, so we'll keep that within the context of the Q&A. But if you did submit a question or we didn't get to your question when you raised your hand, just put it in the basket, and it will be part of the materials that are all in the

Page 18

spirit of trying to collect as much information and input as possible, and same with the e-mails.

Just a couple more things, then we'll get started. Just in terms of the meeting protocols, again, to help support the goals of the meeting, to try and gather as much information as possible; to stay on topic; to be brief with your questions.

I have been in meetings where people have said I have five questions with three subparts for each question. And then you really take up a lot of time. So it'd be great to try to limit the questions that you think are most important for you, and then to be brief in asking questions so we can take as many as possible. And then finally, just as part of that, to be respectful of everyone's time.

Everyone came, an invitation. We're trying to get to hear from all of you as much as possible. And we can express opinions and perspectives in a respectful manner. As Mitch said, there are very strong feelings around this topic, in this area generally, and certainly that's what the request

Page 19

is, that you provide your perspectives and opinions. And we can do it in a respectful manner.

The other thing I would just say, just in terms of helping support, able to hear, is to turn off your cell phones. Or if you haven't already done that, if you could put it on vibrate or something, we don't have musical accompaniment over the course of the day. And then if you also have questions or want to talk to your neighbor, if you could go outside and do that, that would be appreciated, so people can hear the presenters and the questions.

I know they haven't sat in their press seats, but if there is media, please, if you want to have any interviews with any of the CTP staff, you need to go through Raquel Ortiz.

Is she here? I don't see her. There she is. You're standing up, and I still missed you. Sorry.

You can talk to Raquel back there to schedule. For others, if there are media, again, in the room, and I don't know if there are, take

Page 20

any conversations with other non-CTP folks outside the room. We would appreciate that, again, to minimize noise.

Lastly, I would just say I think I mentioned that there will be a transcript. There will also be a docket established soon. So if there are additional follow-up comments from this, or you thought of something getting back to your offices, or on your way, check the CTP website periodically, and the transcript will be up there at some point, and then also a docket to provide additional comment.

So with that, we've gone through the preliminaries of the flow of the meeting and everything else.

Did I miss anything? Okay.

So with that, we will turn to our first presenter this morning, Dr. Daniel Carpenter, who is the Freed Professor of Government at the Department of Government at Harvard University and a member of the IOM committee. So I'll have you come up and we'll get started.

Page 21

Presentation – Daniel Carpenter
DR. CARPENTER: Thanks, everybody, for coming out today. Let me begin. I'm Dan Carpenter. I want to begin with a couple of very important caveats. First off, while I was a member of the IOM committee on scientific standards for studies on modified-risk tobacco products, I cannot today speak officially for that committee. The voice of that committee is the report.
So if there is anything that I say that differs from the very large report that is available in PDF form and is printed, you should trust the report and not me. Okay?
It also goes without saying that I cannot speak today and that the views that I am expressing don't represent necessarily those of the committee. I'm going to try to summarize some of our deliberations. And of course, I'll quote from our report in relevant statute.
What I'm saying today is not necessarily the judgments or the opinion of the Institute of Medicine, separate from the committee, and it

Page 22

certainly isn't the judgment of Harvard University. They've been checking my e-mails to make sure.
(Laughter.)
DR. CARPENTER: Anybody get that joke?
I have done some work in some of this area, funded by a number of related foundations; again, the usual caveat I am going to apply.
So the statutory foundation that I think we're all familiar with here is in Section 911 of the Family Smoking Prevention and Tobacco Control Act. And that section applies to modified-risk tobacco products, essentially, the drug and device approval model that we've seen elsewhere. Not exactly. I want to be clear, this is an analogy. Okay? But the idea is that there's pre-market approval for these products. And the health effects have to be demonstrated a priori.
So the relevant controlling language comes from 911(g), that the secretary can allow these to be commercially marketed if and only if the applicant has demonstrated that such product, as it is actually used by consumers -- which involves a

Page 23

degree of external validity greater than is often seen in the kinds of protocols of studies that we see for drugs and devices -- will first off reduce industry tobacco harm. But second -- and I think here's the really distinguishing key feature, and, again, apologies if you already know this -- benefit the health of the population as a whole, taking into account those who would be likely to use tobacco products and those who would not.
It's that public health standard that distinguishes many of these approval decisions. You can make the analogy, again, to drug and devices. This is, if you will, individual efficacy and safety, which you see in the drug and device world, but this is not in the drug and device world. We don't consider these kinds of spillover effects, if you will.
The other aspect of the statutory foundation is that Congress explicitly gives the FDA authority to regulate the preparation and conduct of the studies issued in support of an MRTP application.

Page 24

This also has a rich history, going back to the 1938 Food, Drug, and Cosmetic Act, the 1963 investigational new drug rules, the statutes that enabled those, the Kefauver Harris amendments, and so forth. So there's a long legal history here.
I think this is key. The committee on which I served was basically authorized in the statute. There are a lot of IOM committees that meet on a lot of things, including tobacco issues and other things. Many of them are called by the FDA without prior congressional authorization.
Part of the charge of this committee was to respond to the FDA, but part of the charge of this committee was in fact to engage in a consultation, which was required by statute, which was required by us. And just to read here, "The consultation is required in statute and it allows the FDA to issue regulations or guidance. But they shall be developed in consultation with the IOM, with the input of other appropriate scientific and medical experts on the design and conduct of such studies and surveillance." Those two terms, I think, are

Page 25

going to be very important as we move forward.
So what happened? Well, again, you all know this. The relevant recommendation is in the list of recommendations at the end of the report. And there is a lot of time that we could spend unpacking the language here, but I just want to alert your attention to a couple of quick facts.
So here's the recommendation as it reads in the published report. MRTP sponsors should consider use of independent third parties to undertake one or more key functions, including the design and conduct of research, the oversight of specific studies, and the distribution of sponsor funds for research.
Such independent third parties -- and I'm going to put my own parenthesis here -- if they are used -- should be approved by the FDA in advance of the research.
So a couple of points on this. First off, IOM recommendations are usually their recommendations. Right? They're not binding guidance. We can't make the rules. We don't have

Page 26

the legal authority to make rules. No committee does for the FDA.
So there are two recommendations here. One is that the MRTPs sponsors should consider using these third parties; and, second, that perhaps not every aspect of the research, but some should be managed by or undertaken by these third parties, including design and conduct of research -- that's, by the way, explicitly an echo of the statutory language -- oversight of specific studies, that would fall under design and conduct; distribution of sponsor funds for research. That would also fall under design and conduct.
Such independent third parties should then be approved by the FDA in advance of the research. Why did we suggest that? A couple of reasons. Number one, the FDA is going to be the one ultimately judging these claims. It's the ultimate -- as I've argued in my book, Reputation and Power, in the pharmaceutical realm, the ultimate veto player over entry into the market. And that's a brute way of describing it, but that's

Page 27

essentially the mechanism by which drug and device approval in R&D in the United States works. That's what's going on here. Probably a wise thing, if you want a third party that has credibility, to make sure that the person reviewing your application as an MRTP sponsor views it as independent and credible.
Second, the FDA is probably going to have a view about what is best -- supposed to have a view about what is best not only for the MRTP sponsor, but also for the public health at large. That's one of its charges under this law. And so it's going to be using, in theory, different criteria and perhaps more appropriate criteria for the selection of independent third parties.
It doesn't mean and we did not say -- we discussed this -- that the FDA should a priori name the third parties. Our recommendation was simply that there may be multiple candidates for a third party, and there are a number of ideas about what this could include, and that the FDA might reject some of those and suggest that some of those are

Page 28

not appropriate, and might suggest that others are more appropriate.
So it's important to understand that – and here I can summarize a few of the deliberations, but, again, to the extent I can't speak for the committee -- when this committee met, the question of governance and how studies would be organized, conducted, funded was very much on our minds. However, the idea of what you would call, say, third-party governance, was a little bit less so, not so much that we thought it was inappropriate or more appropriate. We just had a very open mind.
Some of the very first suggestions for the idea that some of this research should not be conducted and, in fact, would not be conducted in support of MRTP applications from tobacco companies came, in fact, from representatives of some tobacco company units at the second meeting of the IOM committee, which was the first public meeting.
In particular, Lars Erik-Rutqvist mentioned -- and I'm paraphrasing -- at one particular meeting here that, look, there are a

Page 29

wide variety of potential users of these MRTP products, including adolescents, and tobacco companies cannot and should not conduct research on those populations. We would need to find somebody else to do that.

A number of other people echoed a similar sentiment. Now, I'm paraphrasing that, but this letter, which I'm quoting to you is available as an appendix to the IOM report. So if I've mischaracterized anything that Mr. Rutqvist has said -- and I'm not sure if he's in the room here -- in my words, just read the letter.

Essentially, what he said were two things. First, some of this research just won't end up being done by companies, particularly when there are at-risk populations being done. Second, the infrastructure that eventually issues in support of MRTP research must promote public trust and research in MRTPs.

There was widespread consensus at the meeting, which I will explain later, that that kind of public trust, not just -- I'm talking about

Page 30

public opinion. I'm talking about trust in the scientific community, the credibility of research is right now, especially compared to the drug, and device, and other world, lacking in the area of tobacco products, including modified-risk tobacco products.

To go further, in part because of this letter and these discussions, this letter is both important in its own right and evocative of some very important discussions -- again, it's an appendix to the IOM report -- this is Rutqvist, "We hope that the implementation of the Tobacco Control Act will ultimately lead to the establishment of a more trusting environment," -- again, implicitly, one that does not exist now -- "in which stakeholders can share information and perhaps even collaborate on research initiatives.

"We can foresee a time when our scientists and marketing professionals work closely with government and academia in research that is of national, global significance. However, industry should always be merely a contributor and not the

Page 31

lead when studying sensitive subpopulations such as adolescents," merely a contributor and not the lead, always, when studying sensitive subpopulations such as adolescents.

"As the committee prepares its report --" and this, by the way, was sent in August 2012 or '11, excuse me, before the report was issued -- "I hope you will consider the importance of addressing the need for FDA, with support from other stakeholders, to establish an infrastructure that allows for collaborative research, which includes financial and scientific contributions from the industry.

"Again, this is particularly important when conducting research on sensitive subpopulations such as adolescents, the type of research industry will not conduct on its own" -- not "should not," not "may not," "will not." This is his statement -- "due to ethical and product stewardship concerns.

"There are examples of government industry collaboration to draw upon. And he notes one that

Page 32

we also discuss at length in the report, the Health Effects Institute, an independent research organization that provides high-quality, impartial, and relevant science on the health effects of air pollution.

"HEI receives half of its core funds from the EPA, half from the worldwide motor vehicle industry. Since I realize the time has not yet come for the tobacco community to support an HEI-like approach, I certainly think that it or some other collaborative approach is a goal we should strive for."

So here's a problem. Rutqvist's letter refers in part to research on adolescent populations. The problem is, of course, that every MRTP product is potentially consumable, indeed likely consumable sooner or later by one or more adolescents. One or more, I think, is the understatement of the year.

Second, the law requires approval based upon a public health standard. It requires approval considering what are the effects of the product

Page 33

going to be on those who consume products now, tobacco products now, and those who do not.

In other words, at some level, every product is going to have to undergo research on sensitive subpopulations such as adolescents, maybe not adolescents in every single case, but every product is liable -- I don't mean that in the legal sense, but eligible to be subject to research, rigorous studies on sensitive populations.

So this is a much broader point, a much broader application -- and this was also the committee's thinking -- than simply whether or not adolescents were being studied.

Let me advance some further concerns here.

So let me just summarize what I think was the consensus of the committee. And, again, I want to emphasize that in the points I'm about to give you, I'm speaking for myself here. I can't speak for the committee, but I can refer you to points in the report, which basically substantiate what I'm about to say.

Right now, industry-sponsored research on

Page 34

tobacco products is not trusted. I'm not saying it's not trusted at all. It's just not trusted with near the kind of scientific credibility that one sees in devices, drugs, or a wide variety of other medical research.

Two points here. First, that's a finding, not a recommendation, a finding, number 10 of the IOM report, from a wide variety of scientists who are far better qualified than I am as an individual to weigh in on that point; some of them actually from the pharmaceutical industry, top-notch cancer researchers, top-notch OTI researchers, a range of folks.

If you're looking for an example of where that residue of distrust comes from, I would refer to my colleague, Allan Brandt's award-winning book, Cigarette Century.

I mean this as a statement of facts, not as a statement of blame. I know, going into this, although I haven't been working on this theme of research quite so intensively of late, that there are some passionate convictions on multiple sides

Page 35

of this issue. This is not a statement about blame about who's to be responsible for this. It's a statement about where we are. This is where we are. These are the facts. This is an empirical statement of the status quo.

Second, following from number one, the most credible institutions in science and research, including my own university and multiple schools, simply won't accept research funding from tobacco industry sponsors to conduct most trials. There may be in some cases, some particular cases where that has been, but as a general policy, most credible institutions simply will not, which brings us to a problem.

Under the status quo -- and this is something we worried about greatly as a committee -- it's possible that, if you don't have credible research and those health claims are not demonstrated, you don't have a market here, which is to say, you don't have products that ever appear before the FDA, because the FDA must consider these health properties of MRTPs to be credibly

Page 36

demonstrated. That's science. And if the research is not credible, it's not a matter of, well, maybe the FDA shouldn't approve them; the FDA can't. There are definite scientific standards here. That's the same thing, by the way, the same law, which we've had for 50 to 60 years in the area of drugs and devices; that there is a scientific bar which has to be passed.

So to go back, what was the recommendation? Just to sort of unpack it a little bit. Again, the IOM did not consider -- the committee did not consider itself in a position to dictate to sponsors; and, of course, all of its recommendations are precisely that, their recommendations. So we don't make rules.

The MRTP sponsors should consider the use of independent third parties to undertake one or more key functions. It doesn't necessarily mean that all functions of a study or a research program would be undertaken by such third parties.

If they're done, if third parties are used, when they're used, they're going to be more

Page 37

credible and they're going to meet the goals of public health more when they are approved by the -- I just hit the wrong button, so let's go here.

When such independent third parties -- or when the independent third parties are called into action, into consultation, into use, the FDA is the appropriate body from which sanction could issue for the use of these parties. That doesn't necessarily mean legal sanction. It just says, basically, the FDA can give advice on, we think this is an independent third party, high-quality research. By the way, the FDA has done that in drugs and devices for 60 years. There's a long-established administrative legal precedent for the FDA deciding which scientific units are credible and which scientific units are not. Read chapter 4 of my book, Reputation and Power.

So here are some possibilities. I think the first one is the most relevant. It's the Health Effects Institute, and it was created -- not unlike the times we're in now -- in the context of severe

Page 38

distrust, even ideological distrust, of industry research, and on the part of industry, distrust of the EPA.

The idea was, okay, let's have both parties put money into an institute, which doesn't necessarily, by the way -- the HEI doesn't necessarily conduct all the research on its own. It often acts as kind of like NIH review panels for deciding where money should be allocated. It's as much a granting agency as a research university. A lot of universities and research institutes are like that.

It is praised by Rutqvist as a possibility, and it's praised by many others as a possibility. So Rutqvist in his letter specifically mentions the Health Effects Institute as a model that not necessarily should be slapped willy-nilly without thought on this area, but should be considered.

The Reagan-Udall Institute is also mentioned in the report. I'm going to give you, again, my own gloss on this. I think this is somewhat less relevant. It's a possibility. I'm certainly open

Page 39

to it, but there's some big differences here.

Number one, it was also created to advance research in the context of uncertainty. But it's clearly not independent, and, in fact, it's regulated by Congress with a wide variety of sort of positions on its board that are kind of -- it's kind of like the old European corporatist model. You know, you've got one from the socialists, one from the Greens, one from the business and everything like that. That's kind of the Reagan-Udall model.

It's also not nearly as old or as widely respected -- I think that's fair to say -- as is the Health Effects Institute in terms of the legacy, the scientific legacy that it has. That's not to say I think it's disrespected. It just doesn't simply have the benefit and the legitimation of accumulated time and experience yet.

So a couple of additional points and then I can talk a little bit about the special rule, which I know would be of interest, but I can also just

Page 40

conclude.

I want to emphasize two kind of general points. The first is, I know there's been some concern that, why was the IOM recommending this? I mean, this is about how research is organized. This is not about, say, what sort of statistical test to use, what sort of animal models to use, and things like that.

Again, I refer you back to the statute, the design and conduct of scientific studies and surveillance. Conduct clearly includes the organization, the institutional arrangement of research. It has been understood that way in federal law, in federal regulatory practice at the FDA for more than a half-century.

If Congress, in fact, could not and the FDA could not govern the conduct of research, there would be no basis for any law, regulation, or guidance -- and by the way, there are dozens of these sorts of guidances -- from the public health service and a range of others to govern IRBs, and the way they meet and conduct things, their

Page 41

business.
Second, we have to understand sooner or later that regulation constitutes marketplaces. It doesn't necessarily just intervene into a marketplace. It reconstitutes them. And if the MRTP market is to succeed in generating public health objectives, especially in the long run, it has to be trusted, trusted by the public, trusted by the scientific community, trusted by physicians, trusted by public health experts, for that matter, at some level, trusted by investors.
If the research is not trusted -- and this is where I am going to give you my own view, and I'm not saying this is inconsistent with the IOM; I'm just again not going to paste Harvard or the IOM on these; I'm just going to emphasize my own view -- good scientific collaboration will languish. There is that possibility. Rutqvist's letter points to it, again.
Second, products will not be developed rigorously in the way that they often are for medical devices and pharmaceuticals. Applications

Page 42

will not be accepted. The FDA simply won't have the scientific basis or legal basis with which to accept them. And healthy efficient markets, based on information with which people can make sound, informed choices between products and conduct, if you will, optimization, explicit or implicit, among available choices to them will not take hold.
Let me conclude there. If people want, I can talk about the special rule and some of the things that I read there, but I'll just -- thank you very much.
(Applause.)
MS. DILLEY: Thank you very much. So we'll now take some questions for Daniel.
MR. ROSE: Yes. Hi. Jed Rose. I'm a professor at Duke University. And I just had a question about one of the statements that you listed almost as a finding, "The most credible institutions do not accept tobacco industry funding." And two exceptions that come to mind are -- well, one, Duke University; and, second, the University of California system, which had a very

Page 43

extensive debate on the issue and wound up allowing, for example, UCLA to accept tobacco funding.
So did you really mean that there's a ranking of institutions and the most credible ones don't accept, or did you mean most of the credible ones don't accept?
DR. CARPENTER: I want to be a little careful here because we're talking a little bit about academic status hierarchies, and I'm from Harvard, which tends to place --
MR. ROSE: The Duke of the North.
(Laughter.)
DR. CARPENTER: Yes. Exactly.
First off, I didn't -- I mean, this is a generalization and, as I said, there are certain cases -- as I said during the talk, there are certain cases when universities have allowed for those exceptions.
The very debate that occurred in the California case, by the way -- and I think, actually, UVA, by the way, is looking at this, too,

Page 44

so it's not just the two you mentioned.
But the very debate that occurred in the California case points, I think, to the level of distrust and felt need for internal regulation that the University of California system felt that it was needed.
I should point out here that what we do want to avoid -- let me just speak for myself -- is a world where we just have a least-common denominator. So there's one university out there that is willing to accept tobacco money, and nobody else is, and all of the MRTP funding and research that is in support of 911 applications goes through that university or, say, to.
I would not consider that a very credible or rigorous system of scientific organization or of preparation of MRTP applications, no matter what the ranking of those individual universities.
MR. ROSE: Even Harvard?
DR. CARPENTER: Yes, even Harvard. If the only one were Harvard -- and by the way, Harvard had a long history of accepting tobacco industry

Page 45

money for research, so it's not to say that -- you know, I'm not trying to -- this is a holier-than-thou, or we don't do this and everybody else does. I'm talking about a very general status quo.

MS. DILLEY: Other questions for Daniel?

We'll get to you. It's not an easy room to navigate. Go ahead and introduce yourself.

MR. DILLARD: Jim Dillard, Altria Client Services. I was curious about the conversation that you guys might have had, particularly on the governance. Given medical device -- and you alluded to medical device and pharmaceuticals both -- having a lot of history working with the FDA, and the FDA really being the governance structure, what was your conversation between confidence in FDA to be able to pull this off versus the necessity for another third party, who would be really an intermediary between the research that might be funded by the industry and the FDA's ability to be able to act as that governance structure?

DR. CARPENTER: Yes. That's a good

Page 46

question, and I am interpreting it as somewhat open-ended. Let me try to sort of scratch my neurons here a little bit and remember. So I do remember that, in the discussion about the kind of institutions that one might see under this rule. And I really want to emphasize that it's, at some level, open ended, and that is not to say infinitely open ended. But there's room for discretion here on the part of the FDA and on the part of MRTP sponsors, as I'm viewing it, as a committee member.

The kind of arrangement would not be that a third-party structure would govern the research so much. If you look at the HEI, essentially, you put money into a pool, into which by the way the government also puts money. And I'm not saying that that's necessarily what we need to do here.

But they put that money into a pool, and then you assemble something like -- think about an NIH review panel. It's a bunch of people who are just demonstrably independent of the sponsor. And they say, "Who's going to work on this study?" And

Page 47

a bunch of applications come in: Duke, University of California, Harvard. And that entity, HEI, and not the company, decides who gets the contract.

So the idea -- and this is the HEI idea, and I'm just floating this as a possibility; it's not something we said this must happen. But that idea removes the potentiality of an implicit quid pro quo between the company and the potentially repeated recipient of contract research funds.

Keep in mind, too -- and I think this is a real key part about NIH review panels, which I'm just throwing out there for a case of example -- they rotate. So it's not the same people again, and again, and again that a certain university or provost at a high-ranking medical center gets to kiss up to. I'm speaking a little bit casually here. But there have been concerns about exactly that kind of thing.

So by the rotation at some level, you try to ensure that there's a fresh panel each time, which makes these judgments about where the funds should go, and then what the design of the studies should

Page 48

be.

Now, part of your question I think also gets at governance, which is to say governance -- it gets at a number of things. It gets at governance in the sense of what's the organization? What's the funding? It gets at governance in the sense of the nitty-gritty of research design.

We had a lot of discussions about this question about adolescence and other sensitive populations. And that was another case in which we felt that, if there were proposals from research units -- again, universities and others -- coming into this third-party entity, which had this TR -- what's the acronym that everybody's using now?

No, not MRTD. TRGE, tobacco research governance entity; so like the HEI; that they would say, well, look, we think this design, this study design, crossover, whatever, sample size, certain features of the protocol, is appropriate for adolescence and this other one is not.

In part, in the judgment of just acting like

Page 49

the editor of a peer-reviewed journal, by its approval and veto decisions itself, that third-party governance entity, not vetoing the product, but making decisions on the funding applications, would be able to send signals, explicit and implicit, about what sorts of study designs would be better and what sorts of study designs would be worse.

MS. DILLEY: So just to follow up with that, HEI looks at study design. It doesn't look at a particular application for a particular product. It's more the structure of the design.

DR. CARPENTER: HEI and everything we're looking at here is not something that would take the place of the FDA in making decisions on this product. That, I think, is quite clear. This is the design and conduct of research in support of an MRTP application.

MS. DILLEY: So other questions?

MR. WILCOX: Thank you. Neil Wilcox, chief compliance officer for the Lorillard Tobacco Company. To characterize what Jim was saying in

Page 50

maybe a little bit different question, the Food, Drug, and Cosmetic Act requires that any studies that are conducted for a product to be submitted to FDA must be well-controlled.

It's not new to FDA in terms of reviewing proposed studies and protocols. It's what FDA does, and does very well, I might add. It also is not new in the arena of FDA for FDA to be criticized under the notion of capture. And it's not also new for the public to mistrust industry. They just happen to mistrust the tobacco industry even more.

So with that in mind, FDA has been criticized for years for capture, in other words, using the studies that are generated by industry to -- the data generated by studies from industry to make decisions on regulating products.

So FDA then must hire competent individuals to make sure that when they review the protocols for the intended studies, that the protocols meet the requirements of the Act, and that is to be well-controlled.

Page 51

My question is -- and I believe it's the same thing that Jim was asking -- why can't FDA hire and maintain competent individuals to know the difference between well-controlled studies and to make sure that the studies that are proposed by industry to study and develop or generate data for MRTPs -- to make sure that the studies are well-conducted?

DR. CARPENTER: That's a very good question. So I think I have three responses. So the FDA is an old agency at some level, but this FDA is not, which is to say that the Center for Tobacco Products is new, and the architecture and experience of reviewing applications for tobacco products is also new. And the degree to which one can extend FDA's past experience to this field is limited in a number of respects.

First of all, by the nature of tobacco products themselves and the fact that they're not prescribed, the FDA can't rely as heavily upon prescription restrictions or labeling for controlling downstream use.

Page 52

The second, of course, being that -- and I think this is the key -- the public health standard of the law. FDA has never been in the position, before 2009, of examining studies where the critical element of what is affected by the treatment is not simply the individual user, but also a range of other people who might be users or who might quit.

So that's the first thing. I agree that the FDA has been at this kind of thing for a while, but not in the tobacco area, and there are huge differences.

This is different also in another sense. And I guess you're right that we had a lot of discussions about this. We certainly wanted to avoid turning the IOM -- we wanted this to be a scientific exercise, put this way, and we wanted to be consistent with the call, which is to say the callout, the authorization for our activities in the law.

So there are two differences about this sort of area of trust. Part of it is public trust in

Page 53

the tobacco industry and scientific, and you're right that there are differences. There's also a difference in the way that the law has been written and rewritten. And that's in Section 2, which is the finding section of the Family Smoking Prevention and Tobacco Control Act.

There is an extensive discussion in there in that, which are not findings of opinion, which are not statements of judgments. Those are now, by virtue of incorporation into congressionally-passed and presidentially-signed statute findings at law that, in fact, the tobacco industry -- and I'm paraphrasing here, but read it; it's quite extensive, about how this situation is different.

The FDA has the expertise, but -- I choose my words carefully here -- there was a pattern, as I suggested here, of non-rigorous research -- not saying by your company or by any other, but I'm just putting it out there -- and that residue of distrust that I'm talking about is in some ways -- I should have mentioned it in the talk -- expressed more clearly in Section 2 of the

Page 54

findings than it is perhaps even in Allan Brandt's -- I should apologize --but Allan Brandt's book.

Finally, I guess I would say that a third reason that we shouldn't consider that the FDA would just be in a position to weigh in on studies that come from the industry is that the industry itself has told us that in some very important cases, adolescents and other vulnerable populations, they won't conduct them. In fact, that discussion that we had, and those discussions -- and I'm almost certain in this respect that Rutqvist was not the only one to have said this at the meeting, and I've heard it informally from a number of other people.

When one set of companies says, "We're not going to conduct these studies," it suggests, number one, that you need a governance structure. And it suggests, number two, that the companies that do end up on their own volition and organization doing studies on adolescents and other vulnerable populations are probably not likely to

Page 55

be trusted. I'm just going to be frank about that. I think that's where we are. Again, it's not a point of blame; it's an empirical statement of the status quo.

MS. DILLEY: Thank you. We have time for one more question.

MR. DELMAN: Yes. Farrell Delman, TMA. My question is somewhat similar to the last two that you had in terms of the existing governance structures offered by FDA, although it's slightly from a different angle.

As you may know, and as IOM may have discussed, the FDA and NIH are offering a whole series of grants to the various communities out there, and the industry can participate based on the webinar that has held.

I guess it was August, right , Kathy?, I think it was August.

These are R1, R3, R21s, P50s, and so on, are now being made available to address the research priorities that CTP has identified, including MRTPs.

Page 56

So I'm wondering what's wrong with that structure. When you look at that structure that's in place now, involving FDA and NIH, and a grant process, and industry can contribute to it, of course others would as well. And this third-party NIH-FDA would be essentially identifying those projects that they would wish to fund. And it runs through this process that exists already.

What's wrong with that process?

DR. CARPENTER: Nothing is wrong with it. It's just different. It's not the same thing.

MR. DELMAN: No, no. But why would it not be able to address the issues of governance?

DR. CARPENTER: So the NIH process is not for research in support of MRTP applications. It's for the development of regulatory science. So it's for the development of a scientific framework from which a better development, evaluation, and study of MRTPs generally will ensue.

So let's just be very clear here. Nothing in the NCI grants is funding a study that is going to be used in the portfolio or dossier. I suppose

Page 57

it's possible. That's clearly not the intent of the NCI grant. They're trying to say -- by the way, the FDA is doing this not just in the NCI case. There's a huge development right now of trying to improve regulatory science.

How can we develop innovation? How can we, say, think about alternatives to strict randomized controlled frequent trials and import Bayesian criteria. How can we do a range of other things?

I don't think there's anything wrong with the model. It doesn't solve the problem that exists here, that if the companies themselves conduct research, first off, most obviously, on adolescents and other vulnerable populations, it won't be trusted and many companies won't do it.

Second, that in many cases -- in part, again, I want to emphasize that we think that in the long run, MRTP sponsors will be better off going with third-party governance than not. Their research will be more credible. There is the possibility -- this may seem shocking, but actually Rutqvist and others point to it. There's a

Page 58

possibility that through third-party governance, one could get rigorous scientific collaboration between academia, the tobacco companies, and their scientists, and the government.

I don't rule that out. I'm not saying that's impossible. But we're way far away from that right now. And the current NCI grant system is for a different purpose.

MS. DILLEY: So the distinction you're making is the type of research that would be done by a third-party governance structure to help support an MRTP dossier and applications.

DR. CARPENTER: The research we're talking about here is in support of MRTP applications. What NCI is doing is, basically, how do we improve the regulatory science as a whole?

MS. DILLEY: Great. Thank you, again.

DR. CARPENTER: Thanks for your questions.

(Applause.)

MS. DILLEY: Dan, you'll be here until lunch, so maybe at the break, you can answer --

DR. CARPENTER: Sure. Yes, yes.

Page 59

MS. DILLEY: -- additional questions.

So our next presenter is David Dobbins, who is the chief operating officer of the American Legacy Foundation.

Presentation – David Dobbins

MR. DOBBINS: Good morning, everybody, and thanks for having us. I'm here to represent the views of the American Legacy Foundation. And I think we'd be remiss as a representative of the public health tobacco control community not, to some degree, to recognize the controversy that originally erupted within that community when this meeting was announced.

That's because, really, our substantive objections to the IOM recommendation are founded in the very same reasons that that reaction was so poor, which is setting up a facilitated dialogue between public health stakeholders and the tobacco industry creates a basic false equivalency that these two groups are equal partners in the public health mission of the FDA Center for Tobacco Products. The Tobacco Control Act makes clear the

Page 60

aims of this center are to reduce the death and disease related to tobacco use.

The letter by Dr. Ruth Malone and others sets out the reason why the tobacco companies cannot be considered partners or stakeholders in this mission. They are adjudicated racketeers who have intentionally defrauded the American public for decades, which has resulted in a devastating toll of preventable death and disease. The credibility they have lost or the distrust towards them is well-earned.

We share the dismay of our colleagues in setting up that false equivalency, and we were deeply disturbed by the initial structure of this forum. It's because it plays directly into the industry playbook. Trying to coop third parties to get them legitimacy and to "rehabilitate their image" that plays directly into their efforts to whitewash their previous record, which of course are based on decades and decades of evidence.

We note we respect the decisions of those in the public health community who chose not to

Page 61

participate in this workshop to demonstrate their opposition to the FDA's approach, and we would also say we don't have any substantive disagreement with their concerns.

The facts are clear. For many years, the tobacco companies manipulated and suppressed research over the course of many decades as an integral part of the fraud they perpetrated on the American public. But they did much of this through the use of purported third-party independent entities, which they actually created and controlled.

Based on this history, the states demanded and the companies agreed, in the 1998 master settlement agreement, to disband their so-called third-party research arms, including the Council for Tobacco Research, the Center for Indoor Air Research, as well as the Tobacco Institute.

If there is any doubt about the tobacco industry's sordid record, it was dispelled by Judge Kessler's historic and extraordinarily well-documented 2006 decision, affirmed by the U.S.

Page 62

Court of Appeals for the D.C. circuit and left intact by the U.S. Supreme Court, that the major U.S. tobacco companies are racketeers.

With specific relevance to these questions, Judge Kessler set out in great detail the company's concerted strategy of the manipulation and suppression of research, including the use of third-party "entities" to do their bidding.

We strongly recommend and concur with our colleagues who have suggested that if it is not already, that decision should be required readings for all of the Center's staff. We should note, we of course believe the tobacco companies have the right to participate in the regulatory process and make their views known to the FDA. I think we would all agree they have aggressively done so. And they have also aggressively exercised their additional rights to go to court whenever the FDA has acted in a way they disagree with.

But let's be clear. Having a commercial interest in the outcome of the FDA's decisions does not make them a stakeholder or a partner in

Page 63

achieving the FDA's core mission to protect the public health, nor does it suggest or countenance an approach by the FDA to create a false and ahistorical equivalence between the industry and independent science. Indeed, it is the industry's record of obfuscation and fraud that drove this IOM recommendation in the first place.

So as you can guess, Legacy opposes that part of Recommendation 10 in the IOM's report and encourages the FDA to pre-approve third parties to design, conduct, oversee, and/or fund the research required for MRTP applications.

That recommendation, while going through the facts of why there is distrust towards the tobacco industry, seems to ignore the implications of the historic record. Thus, we believe the FDA should not use its limited resources to delve into these relationships, a priori approve them, and thereby facilitate the tobacco company's commercial product research and development activities.

We believe the FDA should instead focus on building its own capacity through internal and/or

Page 64

external means as appropriate, to rigorously and independently review MRTP-sponsored submissions, seek to replicate their data as appropriate, and assure that approvals are given only to applications that advance the public health in compliance with the statutory standards.

I want to go to the IOM recommendation, and it was covered pretty well with the first presentation. And I want to go to why the IOM recommends considering this structure. The IOM grounds the recommendation in its observation that the history of public distrust and the absence of governance in the tobacco industry have created an isolated industry that lacks not only the expertise to produce the necessary range of credible and reliable data, but also the trustworthiness to acquire external expertise and avenues to disseminate acquired data.

The report explains that it raises this history not out of an intent to be attributive or punitive, but it's based on concern for the credibility of the FDA.

Page 65

It continues that, in so far as data generated for the FDA by tobacco companies is perceived to lack credibility, the FDA could find its reputation, its scientific credibility, and its public trust severely compromised and perhaps irreversibly damaged.

It recommends the solution set out in Recommendation 10, which includes in part FDA approval of third-party research structures, to which MRTP sponsors could in effect outsource product research.

We should note that we take no issue with the part of the recommendation, which addresses MRTP sponsors' use of third parties to conduct, fund, or otherwise manage their research. That, of course, would be an option for them anyway, and there may well be perfectly good reasons for a sponsor to do that. Nor do we express an opinion on the use or prior approval of third-party research entities and other regulatory contexts, including the development of general scientific knowledge that may inform the regulatory process.

Page 66

Rather, our views are confined to the IOM's recommendation for FDA pre-approval of third-party entities to facilitate product development research. Given the unique history and challenges inherent in the regulation of tobacco, we do not believe that the FDA pre-approval or other sanction of such third parties is an appropriate use -- response to the difficulties MRTP sponsors, and particularly tobacco companies, which are in fact not the only possible MRTP sponsors,. may encounter in generating credible research.

We have four reasons for opposition. First, in so far that there is a problem with the sponsor's submission of non-credible data, the Tobacco Control Act provides an obvious and common sense solution. Reject the application.

Section 911(g)(1) of the Tobacco Control Act squarely places the burden on the MRTP sponsor to show that the product that's actually used by consumers will both significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the

Page 67

population as a hole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

The FDA is tasked with, and has the authority, to conduct a broad and rigorous review not limited to the scientific evidence submitted by the applicant. The FDA will establish its credibility on this issue by rigorously adhering to the statutory requirements for the evaluation of scientific evidence that is submitted in the support of an MRTP application.

Also critically important is the appearance of the statutory requirement regarding the public availability of applications in order to make the review process as transparent as possible.

On the issue of credibility, we would suggest that nothing would be more potentially detrimental to the FDA than allowing an entity that cannot meet these fundamental statutory requirements to ultimately market an MRTP to the public.

If the product sponsor cannot be trusted to

Page 68

conduct reliable, replicable, and transparent research, it certainly should not be entrusted to sell and profit from a product that is in its essence a delivery device for an addictive drug.

Second, we do not believe that it is an appropriate use of FDA resources, or consistent with its statutory mandate, or congressional intent to facilitate an MRTP sponsor's ability to make the required case of approval. As mentioned earlier, the findings backing up the Tobacco Control Act go into this in detail. Congress understood that the history of tobacco industry health claims is fraught with fraud.

Congress understood that light and low-tar cigarettes have not only not reduced risk, but may have increased tobacco use; that products that purport to lower risk but do not can cause substantial harm to the public health, and that these risks are so high that there is a compelling governmental interest in ensuring that statements about modified-risk tobacco products are complete, accurate, and relate to the overall disease risk of

Page 69

the product.
Thus, Congress concluded -- and I quote -- "It is essential that the FDA review products sold or distributed for use to reduce risks or exposures associated with tobacco products and that it be empowered to review any advertising in labeling for such products.
"It is also essential that manufacturers, prior to marketing such products, be required to demonstrate that such products will meet a series of rigorous criteria and will benefit the population of the health as a whole, taking into account users of tobacco products and persons who do not."
Third, and I'm picking up on Jed Rose a bit here, we believe the IOM report overstates the industry's isolation. It is true that a number of major research institutions do not accept tobacco industry funding, but that practice is far from uniform. Philip Morris in particular continues to be a major funder of scientific research centers. The Duke Center for Nicotine and Smoking Cessation

Page 70

Research is an example. Another is the University of Virginia's Tobacco Research program and, of course, we have discussed the University of California system.
MRTP sponsors have vast financial resources, and we believe will have access to scientific expertise. The key is not access. It's holding those experts to time-tested standards for establishing credibility for their submissions, basing their applications on rigorous, replicable, and publicly available studies that conform to scientific standards.
Fourth and lastly, the FDA must not underestimate the considerable difficulties it would encounter in assuring that a researcher or a research entity is truly independent of the tobacco companies whose product development research it would be conducting. After all, this is an industry that with tragic results has decades of experience in establishing and then expertly obfuscating its relationships with the front organizations that have done its work.

Page 71

There are multiple ways that this global and wealthy industry can funnel money or other benefits, including possibilities of future work and funding, which could influence a researcher's objectivity. We are not casting aspersions on anyone to point out that trust will not be an adequate control.
Finally, even assuming that one agrees, which we do not, it is the FDA's job to help provide credibility to privately-sponsored product development research. It's unclear to us how FDA pre-approval of a research structure would accomplish this. The IOM report details the scientific standards that should drive the design and conduct of studies to be included in MRTP applications.
Clear guidance from the FDA to the industry on these research standards, including transparency of reporting and public availability of data, will improve the quality of studies submitted in support of an MRTP or other product-related application.
FDA guidance will also provide a blueprint

Page 72

for review of MRTP applications, either internally or via FDA contractors, to ensure that the data and results provided by MRTP sponsors meet standards for scientific rigor. An FDA's certificate of approval of a particular entity, review board, or scientist, before any research is even designed, conducted, or conceived, would seem to be, at best, irrelevant to review processes in the particular, and, at worst, indicative of a bias towards approving whatever is submitted.
Thank you so much for your consideration of our views.
(Applause.)
MS. DILLEY: Thanks. What we want to do is, as I said before, for the panel, we'll take one or two questions for clarification. And then, at Q&A, we'll have all panel members from this panel. (Inaudible – off mic.). So are there any questions?
(No response.)
MR. DOBBINS: Thank you.
MS. DILLEY: So next, we have Joanna Cohen,

Page 73

who is the Bloomberg professor of disease prevention and the director of the Institute for Global Tobacco Control at Johns Hopkins Bloomberg School of Public Health.

I also want to remind people, on saying titles and affiliations, that their bios are out -- when you came in -- if you want that information, it's available out at the front desk for your interest, if you'd like to review that.

So with that, I'll turn it over to Dr. Cohen.

Presentation – Joanna Cohen

DR. COHEN: Great. Thank you.

Thank you for the opportunity to speak. Let me cut to the chase and tell you my position, and then I'll go through some of the slides that I've prepared. So, basically, I feel that there needs to be a governance structure for MRTP and other research that is going to be considered by the FDA for the regulation of tobacco products, but I don't agree with the Recommendation 10 as put out directly in the IOM report.

Page 74

I am in my 20th year now of doing tobacco control research. I have many interests. And one of them is the links between tobacco companies and academia.

I'll tell you why I got interested in this, and this was back in the 1990s, when I was working in Canada. And at that time, there was a move to ban tobacco company sponsorship of sporting and cultural events. And we would point to those sports groups and point to the cultural groups that took tobacco company donations and said how awful that was. And I thought, well, before we point fingers at others, we need to look at the dirt in our own home.

That's why I got interested in how universities were basically accomplices in the tobacco epidemic. And one of the commentaries that I wrote, published in 1999, was Institutional Addiction to Tobacco.

I think these aren't my updated slides. Is there another -- let me just see.

I have a schematic that shows -- so I have a

Page 75

schematic from that article that shows a diagram of how tobacco companies can have links with academia. So one is through research grants directly to researchers. There's, of course, donations that go to academic institutions, and as well ties on boards of governors with appointments of tobacco company officials on academic boards.

So a couple years later, I wrote an editorial in the British Medical Journal, Universities and Tobacco Money, indicating clearly that universities are accomplices in the tobacco epidemic.

So there's been a broader recognition -- or with a broader recognition that the tobacco companies have been vectors of the tobacco epidemic, there were several efforts to convene researchers, and policy experts, and civil society to debate the issues regarding tobacco industry involvement and research.

Mitch Sellers referred to a couple of them. Associated with the 2003 SRNT meeting in New Orleans, there was a post-conference symposium that

Page 76

discussed this. And I actually -- and I guess the slide isn't -- oh, okay. Here it is.

This is the schematic that shows the links between the tobacco industry with researchers, industries, and boards of governors. I've addressed those, and they're in the paper.

I wrote one of the background documents for that meeting in New Orleans, and it was published in the TRDRP newsletter in 2003 that outlined some of the issues regarding tobacco industry sponsorship of research.

There was also a session held at the 2005 meeting, SRNT meeting, in Prague -- and I'll just say SRNT is the Society for Research on Nicotine and Tobacco -- and a session associated with the 2005 National Conference on Tobacco, Our Health, held in Chicago.

But I think a number of us got a little frustrated because we felt we were preaching to the choir, and there's lots of talk and not enough action on this front. So in 2007, my colleagues, including one who's in the room today and others,

Page 77

convened an invitation-only workshop at the 2007 SRNT meeting in Austin, where we wanted to discuss various funding models of tobacco-sponsored research and criteria to involve, amend. So the start of that meeting was, is there a funding model where tobacco company money would be used for research that would be acceptable to the tobacco control community?

We didn't come with a pre-supposed answer. We did not invite tobacco company employees to that meeting, but we did make sure to have a range of views represented at that meeting, including people who accepted tobacco company money for research, as well as people who were strongly opposed to that.

So this is the paper that was published based on that meeting, where, based on the discussions and the feedback, we proposed some criteria for evaluating tobacco control research Funding programs with financial support from the tobacco industry.

Of course, all this work and a publication of the paper occurred before the Center for Tobacco

Page 78

Products was even a -- well, it was probably a twinkle in the eye by then, but certainly not set up in before the passage of the Family Smoking Prevention and Tobacco Control Act.

So let me just go through the eight criteria that we laid out. And I want to acknowledge that there is overlap between the criteria as well as they are pretty generic and can be applied to a broad range of research.

So transparency and independence. So the funding mechanism needed to be transparent and independent with an application process that was explicit and clear with scoring criteria, of course with peer review, and reviewers would not be tobacco company employees or contractors. The funding process had to be competitive, again, with using peer reviewers with relevant experience. So this is not sole-source funding.

Clearly, there would have to be provisions for ownership of data and freedom to publish results. The research agenda would have to be set independently of the tobacco companies because

Page 79

there is an acknowledgement that a funder can influence an agenda even when there are no strings attached. So there is a sense of obligation and awareness of priorities and possibly expectation of future funding. And, of course, this particular criteria is going to be a little more challenging with Section 911 because the agenda is sort of set. But this is one of the general criterias that we outlined.

We talked about governance sort of broadly, proposed a transparent and effective governance structure to oversee the funding that took place. We also thought that there needed to be adequate protections in place to guard against potential conflicts of interest. There would be a written conflict of interest policy, mechanisms for enforcing that. And not only would there be disclosure of potential conflicts of interest, but also some relationships might have to be prohibited.

So there's a huge challenge with tobacco industry funding, that this research -- and my

Page 80

colleagues have addressed it -- has been used for public relations gains that counteract public health. So companies have gained respectability and credibility by association in funding this funding research. So the funding model would have to ensure that there is minimization of the PR gains that counteract public health.

Then our last criterion at the time, because this was thinking within a vacuum at the time, was that the model had to -- one of the criteria was that it had to be feasible that it could actually happen.

So we applied these criteria to four different models -- it's in the paper, so I won't go through it -- and then we held another meeting at the 2010 SRNT meeting to discuss the criterion and see what the next steps were. And at that point, we knew about the new tobacco act, and we put things on hold for a bit.

But let me just go through the criteria in the IOM report that are laid out for the design and structure features of a TRGE, which is one of those

Page 81

new acronyms that is a mouthful. So that was a tobacco research governance entity. I think that's the terminology used in that report. So the criteria that the IOM report lays out is that the funding could be public and private funding. There would be an oversight board that would be independent of the FDA and tobacco or MRTP companies, and there would be conflict of interest policies.

The research design would be independent of the sponsor. There would be organization, oversight, and training, so the research performance would be monitored. There would be IRB training and data monitoring committees. And there would have to be some sort of contract mechanism, either a request for applications or a contract. And there would be quality control, including audits.

So I just put together a paper or a table to try to compare the IOM features of a governance structure and the ones that we had thought about. So the funding, we dealt with separately. The

Page 82

oversight board corresponds to the general governance that we talked about in protection against conflicts of interest.

The research protocol advice that the IOM suggested, we wrote up as transparency and independence, including an independent research agenda. We didn't discuss explicitly organization, oversight, and training, whereas the IOM talked about contract mechanisms. We were very clear about a competitive funding process.

We didn't address quality control per se, and then we talked about things like ownership of data, freedom to publish, and addressing and minimizing industry PR gains that counteract public health that were not explicitly addressed in the IOM report.

So a couple of concluding remarks. From what I can tell in the IOM report, it talked about independent third parties, plural, so my proposal is for one governance body to oversee all CTP-related product research. I'm not sure what exactly pre-approval means, but all research will

Page 83

still, even with this, need to be critically evaluated by the FDA and CTP. So just because we have this structure in place, it doesn't mean that this is gold standard science. It still needs to be critically evaluated.

If, for once, a third party structure is set up, its structure and processes need to be reviewed regularly. There needs to be periodic external oversight and review by a prestigious external group, would also be important.

A couple of additional issues to consider. We do not want to be in a situation where the American taxpayer subsidizes research and development work for tobacco products. So whereas the IOM talks about public and private funding, I don't see public funding going into this type of funding model.

I think a proportion of the research funding budget of a funding model of this kind should be spent on broader tobacco control research beyond MRTPs and perhaps even on important topics that are outside the direct mandate of FDA. And there are a

Page 84

number. And then the funding mechanisms and governance structures need to be acceptable to the tobacco control community, so these discussions really need to continue, and a lot of thinking is still needed to work through these issues.

So I think that's it for me.

MS. DILLEY: Thank you. Thanks very much.

DR. COHEN: Sorry. There were a couple of others. I think Daniel had this as well. It's been a while since I've seen the slides.

So I'll just say -- I mean, all this is really important because -- credibility of the research was mentioned before. The researcher needs to be credible, and I think my colleagues will address this further, but there are certainly challenges of taking tobacco company money for research. And we don't want the same people doing the -- the same old folks doing this type of work. And we want our colleagues to be credible members of the tobacco control research community, even if they're doing some important work in this area.

More and more journals are not accepting

Page 85

articles that are sponsored with tobacco company money. We've talked about institutions that don't take tobacco money. So we want to make sure that the researchers remain credible and not ostracized from the community. The research itself has to be credible because, if it isn't, the credibility of the Center for Tobacco Products and, more broadly, the FDA is at stake.

So, again, the funding model and governance structure needs to be thought out very clearly, a lot more discussion, and I think imperative that we figure out a model that is acceptable to the tobacco control community so that we can move forward together.

(Applause.)

MS. DILLEY: A couple of questions for Joanna before we go to break?

DR. CARPENTER: I'm generally loud enough that I don't need one of these. The slide where you say what the entity will do, are you contemplating an entity that sets up rules for the conduct of research or a third-party entity that

Page 86

conducts that research itself through employees, grantees, et cetera?

DR. COHEN: No. I see the FDA is setting up the rules for the research. And this third party, as I see it -- and this just starting points, so this needs a lot more discussion. But as I would see it, they would not conduct the research. It's just a flow-through for a competitive funding process.

So money would be put into this funding model with the governance structure. When there's research to be done, people can apply, and then it's a structure to review who can do the research and what the strongest proposals are.

DR. CARPENTER: That's what I thought. And just one brief follow-up -- and I won't go into part B -- what advantages would that third-party entity provide, over the FDA issuing contracts for research, that it wanted to follow up through approved government funding mechanisms such as grants or contracts?

DR. COHEN: Yes. That's a really good

Page 87

question, and I think I have to think through that carefully. As I sort of hinted, I would like to see this as broader, and not just -- potentially could see a funding model that actually funds other very important public health research and provides a mechanism for that.

So while contributions go towards looking at the minutia of product changes, we can also do some of the population health work that needs to be done.

MS. DILLEY: That's the public health research, but that scope is broader than the MRTP research we're talking about.

Anybody else have a question for Joanna?

(No response.)

MR. DILLARD: Jim Dillard, Altria Client Services. Dr. Cohen, thank you. I had a question, actually, for FDA and then perhaps a question for you, which is, it appears from an industry perspective, as I'm thinking about -- sort of applications, as an example, you would think about perhaps having to do some sort of clinical

Page 88

research, perhaps in a substantial equivalence type of application, definitely in a 910 new product application or a 911 MRTP application, where industry would be thinking about research to support an application for a product where it will meet the statutory criteria, but also perhaps be of some benefit both to public health as well as industry interests as well.

So the question I'm having going through my head is, are we talking about here a broader topic of third-party governance or governance just for the purpose of an MRTP application? Because what I could envision potentially -- and maybe this is what you were getting at a bit, Dr. Cohen -- is that there could be different models for different application purposes, the model that you put forward, the model that the IOM put forward.

So one of the questions I've got for the agency is, are we talking broadly about third-party governance or are we talking about it more specifically for an application type of purpose? Which is where my head was when I came in here.

Page 89

MS. DILLEY: You mean as specific, this workshop?
MR. DILLARD: Yes.
MS. DILLEY: So the frame is around the MRTP report, but I think -- and we've already gone there to think more broadly.
So the starting point is the MRTP report and the IOM's report on the third-party governance, but, clearly, it's not a big leap to go more broadly, if you want to address that.
So one more -- we'll take a break a little bit early, and that actually would be helpful, because we have a panel of three speakers as opposed to two for this section. So we're happy to take a break early. But one more question, and then we'll take a break.
MR. ROSE: Jed Rose again.
MS. DILLEY: Could you use the mic? People are watching on line. And also, a warning for those of you who ask questions and speakers, they're asking for interpretation -- which you already did, Joanna, so thank you -- of acronyms.

Page 90

So any acronyms, please say what it is first, and then you can use it.
MR. ROSE: Jed Rose. Could you just elaborate a little bit more on what you might mean by the various standards being acceptable to the tobacco control community? Because there's quite a diversity of opinions within the "tobacco control community."
Are you thinking of a majority vote, or what does it mean to be acceptable to -- we obviously want to avoid any kind of groupthink mentality. So what would that mean?
DR. COHEN: Thank you, Jed. And I want to thank you for being part of this meeting and an active participant in the meeting that led to the paper on the criteria, so thank you for being there. I mean, that's a rhetorical question. It's good to have diversity of views. I'm glad that the FDA is starting to discuss this and has initiated this discussion. And I think it's going to take more discussion to figure out -- to debate and to think about how to move forward, so that's the best

Page 91

answer I can give you at this point.
MS. DILLEY: I assume that's where the criteria came from in terms of just what it might look like to at least start that conversation.
Why don't we take a break? It's 20 after. I want to thank Joanna again, David, and Daniel Carpenter. And we will resume at 25 of.
(Whereupon, a recess was taken.)
MS. DILLEY: If everyone could take their seats, we'll get started. Just two quick comments. One is I neglected to mention in the overview of the agenda earlier, that there's one error on that. Tomorrow, for the time, you'll see at the break, you thought you were getting a really long break, 10:00 to 10:45, but in fact, that's only 15 minutes.
So that should be 10:15. I mean, that's important because, obviously, to try and put five speakers in an hour was going to be challenging. So we just added a half an hour to that.
So just so you know, in case you had elaborate plans for that break, you have to change

Page 92

them. So 10:00 to 10:15.
I just wanted to mention that, and also just remind people, please, there are about, I think somebody said, about 95 people listening by webcast, and they really are asking for clarification on any acronyms used, which any area is riddled with that. But if people could give the full name, and then, if you want, for the rest of your comments to use acronym, that's fine.
So next up, we have Matt Myers, who is the president for the Campaign for Tobacco-Free Kids. And, again, then we'll go on to Mark Parascandola and Eric Donny before we take a break for lunch.
So, Matt, with that, we'll turn it over to you.
Presentation – Matthew Myers
MR. MYERS: Thank you, Abby, and thanks to all of you at FDA for holding this session. The advantage and disadvantage of not being the first speaker is, I'm going to try to adjust a little bit what I say so that I just don't repeat what everybody else has said in that respect. So I

Page 93

apologize if there's one or two things that appear less smooth as a result of it in that respect.

But let me summarize our conclusions at the Campaign for Tobacco-Free Kids. First, Section 911 of the Family Smoking Prevention and Tobacco Control Act does address a very critical issue. And that is that for more than 50 years, the tobacco industry has used the promise of potentially less hazardous products, not to actually reduce risk or reduce the number of people who die from tobacco use, but to keep their market share and to keep people smoking with what we now know are truly tragic results. And that is more people smoking, fewer people quitting, and literally millions more people dying as a result of the conscious direct decisions of the tobacco industry about how it is used, the whole potential of the Holy Grail of a less hazardous tobacco product.

Section 911 doesn't prejudge whether there is actually a role for modified-risk tobacco products. What it does is seek to impose for the

Page 94

very first time in our history a rigorous scientific standard and set of criteria to address that issue, so that we're no longer at the whim of an industry that has been willing to say and do anything to keep people smoking without regard to the health consequences of that. That's the history. That's what brings us to this point in our time. We lose sight of that history at our peril.

Second, we at the campaign strongly endorse 11 of the 12 proposals by the Institute of Medicine, those proposals that focus on the scientific criteria, proposals 1 through 9, about how studies should be conducted, the type of studies that should be conducted, the type of rigor that ought to be applied to studies that should be conducted.

Having said that, we do not support IOM recommendation, at least the component of it that focuses on pre-approving independent third parties to the extent that it relates to research tied to specific MRTP, modified-risk tobacco product,

Page 95

applications. We think that there is an inherent conflict with regard to that.

The tobacco industry's abuse of science, the scientific process, third-party institutions, and some of our nation's most credible scientists at this point, is beyond debate, and it is part of the elephant in the room any way you cut it.

For 50 years, the tobacco industry has claimed to be interested in rigorous science. It has claimed to be interested in reducing the number of people who die from using its product. It has claimed to be interested in supporting independent third-party research as we go on.

Time after time, however, the evidence now demonstrates that they've corrupted science, they've produced products that people have believed are less hazardous, but have done nothing more than keep people smoking. And to a degree that many of us would like to think is impossible, they have corrupted some of our most credible institutions, not because those institutions are bad but because those institutions didn't recognize the extent to

Page 96

which an industry was willing to go to promote its product without regard to the consequences.

Therefore, it is our view that, if IOM Recommendation 10 is intended to provide pre-approval to an independent entity linked to a specific NRT application, then we think it is a fundamental idea and, in the long run, will end up undermining FDA's authority, as David Dobbins had said.

I don't want to spend a lot of time quoting all the things. I have submitted to the FDA a much longer document that tries to lay out the things. But the things I'm saying are not in dispute, as Judge Kessler found. Over the course of 50 years, defendants -- and by that we mean many of the same companies who are in the room today -- lied, misrepresented, and deceived the American public, including smokers and the young people they avidly sought as replacement smokers, about the devastating health effects of smoking and environmental tobacco smoke.

How do they do it? Judge Kessler found that

Page 97

they suppressed research. They destroy documents. They manipulated the use of nicotine so as to increase and perpetuate addiction. And they abused the legal system in order to achieve their goal, to make money with little, if any, regard for individual illness or suffering, soaring healthcare costs, or the integrity of the legal system.

That's the context in which these decisions get made. We would all like to believe that we live in a utopia, but that's not the situation. We'd all like to believe that there is an industry out there who really shares, at least at some level, a concern about the public health. But you can go back as far as the original, the original frank statement made by the tobacco industry 50 years ago, over 50 years ago, in which they said, "We are committed to sound science. We will promise you an open and transparent process. We will promise you that we will act on that science."

We can show you quote after quote from tobacco industry executives that, "If it can be proven that our products cause lung cancer, of

Page 98

course we wouldn't sell them."

What does that demonstrate for the process we've got here? It demonstrates that, in fact, while Professor Carpenter can say carefully, "We're not assigning blame for the lack of trust," indeed, if we fail to recognize the source of the lack of trust, then we are really truly fools after a fool errand, not willing to learn from history.

You're going to hear tomorrow, as we've heard for a year now, that the tobacco industry is once again truly concerned about independence. No one should be fooled. No one should believe it. It is actions that need to count in this case.

They have mastered the words. They have said them time and time again. And nonetheless, time and time again, what we have seen is that they have been willing to corrupt science, scientists, and scientific institutions.

Therefore, what is our recommendation? FDA's top priority should be to establish rigorous scientific standards that all applications under Section 911 should meet, including governance

Page 99

concerning the scientific process, that guarantees openness, that guarantees transparency, that provides the best possible protection to the FDA, that the tobacco industry once again hasn't manipulated the scientific process, the scientific methods, or carefully, as they have so often in the past, designed experiments that they already knew the answers, and therefore were simply producing data to continue to distort the true scientific truth as we move forward.

I don't see and we don't see a reason for FDA to set up a special set of rules for the tobacco industry. The reality is that when anybody has tried to do that, it has become the tobacco industry's roadmap to continue its deception. That's not the job of the FDA.

Professor Carpenter talked about how other industries have adjusted in the past when new rules concerning pre-approval came in to place. This isn't a new concept, although it's new to the tobacco industry.

Yes. In the pharmaceutical industry, some

Page 100

companies develop truly credible institutions for pre-approval and others did not. And the ones that did not, did not survive, but that is the way the marketplace is designed to work when we put a priority on saving lives and health. It should be the same case here.

There are, however, even when you do that comparison, some important distinctions between how the pharmaceutical industry responded to pre-market approval and the tobacco industry, that are relevant to this consideration. I think that's important.

As Professor Carpenter in his book said, whatever the tension is between the FDA and the pharmaceutical industry -- and this isn't a direct quote, so, Dan, I apologize if I get the thrust wrong, but I don't think so. What he said was that the pharmaceutical industry knows that it cannot survive if it loses credibility with the American public or with the regulating agency. Thus, it has a great deal at stake in maintaining that credibility.

Page 101

The tobacco industry, on the other hand, has been able to sell its product to the public even though there is no industry held in lower esteem. Why? Because its primary market is kids, its product is addictive, and it has been able to work behind closed doors to ensure that that addiction is all powerful, moving forward.

Second, the tobacco industry has already set a very different tone with the FDA, not the one you're going to hear tomorrow. But the truth is, the facts already show that tone. They will not depend on credibility with the institution. They'll depend on fear. They will sue the FDA -- and they have demonstrated it already -- the second the FDA does something not wrong, but that threatens their marketplace. So the facts don't show a changed industry.

The facts don't show a changed industry. The facts show an industry working off of the same game plan that we have seen for decades, and decades, and decades.

There are real values to an independent

Page 102

third-party advisory body on research to look at broad questions, to look at the industry tactics that have made their products so appealing to adolescents, and to look at the kind of marketing that they continue to do that makes their products appealing to adolescents. But not to provide a roadmap that says, "This product is okay and is not going to be used by an adolescent."

There's another critical fact that goes to that, and that is -- Professor Carpenter talked to us, that there is a unique component to this legislation that requires you to look at not just the toxicity of the product, but whether that product is going to appeal to a broader range of the population. And the research under Section 911 can't just focus on the product narrowly. It also has to focus on how it's going to be marketed, which is truly a different thing, as you look about this.

One product could be marketed truly to adults, but the reality itself up to this point in time is virtually all of the tobacco industry

Page 103

marketing is designed to make tobacco products and different tobacco products highly appealing to young people, attractive to young people because they know what we know. And that is, if they don't catch them young, they're probably never going to catch them.

That leads us to the last conclusion, and I think this is a very important distinction between the tobacco industry and the other industries regulated by FDA. And that is, FDA was created and looks at pharmaceuticals to solve problems that aren't caused by the pharmaceutical industry. Therefore, the path of producing drugs is critical to solving a problem that would otherwise exist.

The Center for Tobacco Products is dealing with an industry that is the cause of the death and disease and whose financial interests, to this point in time, they have always perceived to be, "How many products can we sell," not, "How safe are those products?" So it is a very different kind of interaction. The pharmaceutical industry will thrive on solving a problem. To date, the tobacco

Page 104

industry has thrived by causing the problem.

So the notion that we can expect the tobacco industry suddenly to turn around, and change its stripes, and become part of the solution is something we should look at with a great deal of hesitancy. There is nothing we have seen in the tobacco industry's response to this act, to their rhetoric, or to their behavior, that says it's time for us to trust them. It is time for us to ensure that we have a regulatory agency that operates independently but fairly, rigorously, with one goal in mind, and that is, "What actions will save the most lives, not promote the most products?"

If the tobacco industry can meet those standards, then fine. If it can't meet those standards, then Section 911's main contribution may well be simply to prevent them from continuing to do what they have done for 50 years, which is use the hope of a potentially less hazardous product to keep people smoking. Thank you.

(Applause.)

MS. DILLEY: So we just have time for one or

Page 105

two questions.
Can I ask you a question?
MR. MYERS: Sure.
MS. DILLEY: It seemed like the combination of third-party governance that you mentioned has a role in some things, but the combination of pre-approval by FDA and the fact that it supports an application is where there is a particular problem.
MR. MYERS: Exactly. I think, if you do it, is linked to a specific application. What we've already seen is that those of us who have been concerned about what application has been filed, that process isn't transparent until too late in the process. If it was going to be an open and transparent process, maybe there would be something that one could talk about. But right now, it operates behind closed doors until very late in the process.
Second, I think that there is an inherent conflict. And what we have seen is, in this case, when somebody identifies an institution -- Harvard

Page 106

is a fabulous example for Dan, incredible institutions. I mean, NCI after the first Surgeon General's report came out, we had the Tobacco Working Group, a process that got incredibly corrupted, focused on less hazardous cigarettes rather than focusing on what are the harms caused and how do we stop them.
So we all like to think that we can build institutions that are impenetrable to corruption, but you can't do it when you have an industry with a mindset, that our sole goal is how do we maximize our profit, no matter how many people we kill? And to this date, that's what the tobacco industry's mindset has been.
MS. DILLEY: One other question, Dan, and then we'll go on to the next.
DR. CARPENTER: Thanks for the excellent talk. I just want to clarify, because I think what I'm understanding is your -- and I'm forgetting the gentleman who spoke earlier before --
MR. MYERS: David Dobbins
DR. CARPENTER: -- David

Page 107

Dobbins's -- thanks -- primary concern is about the idea, basically, the FDA approving these third-party governance organizations or institutions, and that the concern is a little bit less with the idea that there should be some separation of tobacco funding and the actual research or the research institution that's conducting it.
Is that an understanding of where your primary objection -- I'm not speaking for him, but the primary objection to Recommendation 10.
MR. MYERS: Yes. I can't speak for David. Pre-approval is our highest priority in terms of the concerns with regard to that. I would think that there would be issues that relate to "a specific narrow product" as opposed to some broader use of the third-party funding for a broader set of questions that will relate to the issue of Section 911, so that you can address them broadly.
In the examples you talked about where the industry said -- and I can't speak to Swedish Match, but I've heard industries say before, "Gee, we don't do research on young people because that

Page 108

would be unethical," only for us to discover in their own internal documents just the opposite. But I do think that there is a role to play for maybe a third party to look at. What parameters would we have to put on it to make sure that it didn't impact young people in that respect and come up with a set of guides. My suspicion is, if the tobacco industry didn't like the results, they would attack them, too.
DR. CARPENTER: Yes. So I want to just follow up just to clarify a little bit of what my own thinking is on this. First off, I think it's quite possible you'll still disagree with what I have to say and that Mr. Dobbins will as well.
But I think just one quick thing is, number one, I think the recommendation is sufficiently general as to include, as possibilities, for instance, what Dr. Cohen presented earlier, the idea that what really is being approved here is at some level a larger entity, to which could become kind of the go-to model for individual product funding decisions and things like that. I'm not

Page 109

recommending that as the only thing, but the IOM's practice in many cases such as these is not to pinpoint a very, very particular kind of model to be used.

So I think what may be kind of inducing some disagreement is the plural here, the idea that the third-party institutions or the third-party organizations, as opposed to a general HEI-like organization, should be in operation.

So I want to emphasize that it's not necessarily the case that the recommendation would set up 200 different third-party institutions. It is quite possible that it's consistent with just one.

But I want to emphasize one other thing about -- and this is just an argument against or at least to sort of temper a little bit of the doubt about pre-approval.

We thought about this. At some level, this entire regulatory structure, not just Section 911, places the FDA in a situation where the credibility of an institution that, relative to a wide variety

Page 110

of institutions, has had some over the past 50 to 60 years -- thank you for saying my book; I'll donate the --

MR. MYERS: I recommend everybody in the room read your book, so that's all right.

DR. CARPENTER: -- but where it's had it, and so we're concerned about this. But let me just be very clear that at some level, again, the FDA does a good bit of this.

Now, third-party institutions, specifically no, but if I just look at the pharmaceutical world, initial approval of protocols, essentially, CDER does that, if not with a wink and a nod, in pre-phase 1, pre-phase 2 meetings. Approval of protocols for phase 3 clinical trials at end of phase 2 conferences, they do it already.

And any time, essentially, the FDA lets an IND, which is an investigational new drug application, run out into the market without halting it later, they are giving their implicit sanction to at least the study design as potentially indicative of -- or as potentially

Page 111

revelatory of the efficacy and/or safety of the drug.

MS. DILLEY: That's public information?

DR. CARPENTER: That's public information, all those. I don't know whether every aspect of end-of-phase-2 conferences is because those might be protected by trade secrets. So there is often, by the way -- there is an exception to the Freedom of Information Act, whereby certain features of a not-yet-approved drug product are not available for the public. But that's a whole separate area of law.

But I just want to emphasize that none of that prevents the FDA in the pharmaceutical world from asking for more data later on, saying that the conduct of the study or that the study, once completed, even though we thought the protocol was fine at the time, raises more questions than in answers, and as pharmaceutical companies and all sorts of people will be happy to tell you, reject repeatedly and delay repeatedly -- and I'm not saying for good or bad reasons. I think, quite

Page 112

possibly, the public health is served by these decisions later on.

So I'm a little doubtful of the claim that by just giving a thumbs up to the go-ahead with a third-party study, the FDA is somehow committing itself to approving the product.

The experience we have from 50 to 60 years of pharmaceutical regulation, in fact, if anything, the opposite occurs, much often to the consternation of the industry in that field. Maybe this industry is different, but I just want to put that out there, that I don't see a hard link between those two.

MR. MYERS: I see what you're saying, then. A couple of distinctions that I think are important, one of which is, we explicitly endorse the idea of FDA spending a great deal of energy in coming up with their recommendations about study design and the like with regard to that. We think that's absolutely fundamental, more fundamental here even than with the pharmaceutical industry because we've just seen repeated examples of the

Page 113

industry producing science designed to show that its products don't cause harm or that particular additives don't cause harm, which subsequent independent review after publication has demonstrated that the science was flawed, and probably intentionally flawed to be honest with you.

So that sort of activity is something that I think we're supportive of and is more necessary here, I think, than it is even with the pharmaceutical industry because of the abuse that the industry has done up to this point in time.

What we object to is pre-approving not study design but entities that would be deemed to be in advance credible because of the history in this case of a willingness to abuse institutions. And I'm not actually critical of the institutions because I think they got taken by an unscrupulous industry, because they operated with innocence and belief in the scientific process.

DR. CARPENTER: That's naive.

MS. DILLEY: Obviously, it's a bigger topic

Page 114

and you're not going to be here this afternoon in Q&A. So I'm glad you raised it because it's something that the rest of the panel can also address.

I'm going to hold your question, Corinne, if you can wait, because we've got two other presenters. So Matt, thank you very much.

MR. MYERS: Sure.

(Applause.)

MS. DILLEY: Next, we have Mark Parascandola, who is an epidemiologist in the Division of Cancer Control and Population Sciences at the National Cancer Institute, National Institutes of Health, and Dr. Parascandola will be giving this presentation now. And then also, after the model presentations this afternoon, we'll help start up the conversation around translation into the tobacco arena. So thank you very much for doing double duty today.

Presentation – Mark Parascandola

DR. PARASCANDOLA: Thanks. Good morning. So I was also at that meeting in New Orleans around

Page 115

SRNT over 10 years ago, and that was one of my first forays into the world of tobacco control, and I've been hooked on it since then. So, hopefully, that means the meeting was a success. And I was also among the co-authors on the paper on tobacco funding models that Joanna introduced.

But in my remarks here, I want to address a couple of other elements of this issue. First, is to just point out some lessons from history that I think are important to remember, to understand the nature of the distrust that exists around tobacco industry funding of research and also involvement with the research community and, secondly, to show how the lack of trust really goes beyond the conventional concerns we have maybe in other areas of biomedical research around potential conflicts of interest. So they are, therefore, maybe requiring special attention.

So, in particular, the concern here is not just about the validity and integrity of research results -- which is often our concern when we talk about scientific integrity, we're concerned about

Page 116

biased results and this sort of thing -- but also about the nature of the relationship between the tobacco industry researchers and public health authorities and how that relationship has sometimes been misused.

So following the release of the 1964 report -- this is kind of the first episode I wanted to bring up. Following the release of the 1964 the Surgeon General's report on smoking and health and efforts to begin controlling cigarette labeling and advertising, senior staff members of the Tobacco Institute, which was at the time a tobacco industry trade organization, went about "seeking dialogue and scientific cooperation --" those are their words -- with senior officials in the Department of Health, Education, and Welfare. And here is an excerpt from one of the internal industry documents talking about this effort. But according to their planning notes, the Tobacco Institute intended to propose the creation of a central agency for tobacco research with joint oversight from government and industry, so that

Page 117

both groups would -- and these are their words again -- "speak with one set of figures."

As explained in their memo, one of the motives for this effort was the understanding that scientific cooperation between industry and government, or at least the appearance of cooperation, could diminish the basis for -- again, their words -- "reckless and untimely regulatory action."

Tobacco industry president Earle Clements met with HEW's secretary at the time, John Gardner, and then subsequently his successor, Wilbur Cohen, a number of times from 1966 to 1969 to discuss collaboration in this area.

So one of the things that came out of this effort was there was a joint committee on tobacco and health that was established in 1968, including representatives from the National Institutes of Health, the industry-run Council for Tobacco Research, and the American Medical Association's program on tobacco and health, which was also funded by the tobacco industry. And over a number

Page 118

of years, this committee met and discussed various research needs and tried to develop a joint statement.

They were unsuccessful in doing so because they couldn't agree on the language. They couldn't agree on background language to set up the document. And, in particular, the Council for Tobacco Research and AMA research program representatives objected to language inserted by NIH, which summarized the current state of knowledge on smoking and health, based on the Surgeon General's reports and other information.

So there was no document that came out of this effort, but the tobacco industry did gain positive publicity via public statements from senior government officials highlighting the many research gaps that still remained on smoking and health and also highlighting this government industry collaboration in the area.

The second episode I want to mention, at the National Cancer Institute, starting in 1968, there was a working group formed to begin to do research

Page 119

around what was called at the time less hazardous cigarettes or potentially less hazardous cigarettes. And the working group included representatives from academia, government, and also the tobacco industry. And I have highlighted in red here three senior research officials from R.J. Reynolds, Lorillard, and Philip Morris. And the folks on here were among some of the longest-running members on this panel.

This effort continued over a period of about 10 years, and I don't have time to go into all the details here. But I wanted to point out that the tobacco industry benefitted in several ways from their participation in this effort. First of all, they gathered information about developing public health service research initiatives in thinking around tobacco that was not otherwise public. Industry representatives also sought to influence the direction of research programs and discourage research in certain areas.

They also gained an appearance of cooperation with government officials and

Page 120

benefitted from the semi-official endorsement of the low-tar cigarette strategy. And at the same time, industry representatives did not share much critical information about their own research on nicotine dependence and smoking behavior at the time, which could have certainly been of direct relevance to this effort.

Finally, the fact that the tobacco industry was producing cigarettes with lower tar and nicotine content at the time, as recommended by the tobacco working group, may have helped to stave off more rigorous regulation and control of tobacco products during the 1970s.

So I think, in sum, the tobacco industry really benefitted much more from this relationship than the public health community did.

The second component here that I wanted to address is how the concerns around trust in tobacco industry-sponsored research are different from those in thinking about other kinds of research such as research funded by the pharmaceutical industry. Formal attention to conflicts of

Page 121

interest and research integrity are really relatively recent. I think it's the increasing commercialization of biomedical research in the 1980s that led to a lot of these policies that are now ubiquitous in research institutions.

The concern at the time was that, under some of the academic industry collaborations that were developing with the growth of biomedical research in the 1980s, and suddenly academic scientists and institutions stood to gain financially, to a much greater degree than ever before, from the commercialization of research products.

So a number of universities and scientific journals developed policies to address potential conflicts of interest. And the primary mechanism that's used is requiring disclosures, either annual disclosures of outside activities, disclosure when publishing a paper of sources of funding, and this sort of thing.

Then in the following decade, during the 1990s, as litigation and investigation of the tobacco industry progressed, there are a number of

Page 122

academic institutions put into place, new policies restricting acceptance or refusing acceptance of tobacco industry funds.

But the content of these policies was very different than the conflict of interest policies that we saw from the previous decade. And instead of focusing on concerns about bias or commercial influence on interpretation of results, the rationales really were stated more around the clash of values and goals of industry versus the academic institutions.

I've quoted from a few of these academic policies on tobacco industry funding. And I point out how the extent of disease, disability, and death caused by smoking and the conduct of the industry are so completely at variance with the stated mission of the school: incompatibility with the public health mission; any association with the tobacco industry taints the reputation of the college; tobacco companies produce a product and have behaved in a manner that are at cross-purposes to our academic mission.

Page 123

So the tenor of these policies and their intent really is very different. And in fact, in 1994, the National Cancer Advisory Board actually included a recommendation in its report to Congress proposing to withdraw federal funding from cancer research organizations that accept tobacco industry support. That never happens, but it shows you the sort of level of concern there was about this issue throughout the public health community and the cancer research arena.

So these academic policies really single out the tobacco industry as different from other industries. They differ qualitatively from the conflict of interest policies. And in addition to their intent, most university conflict of interest and research integrity policies include specific mechanisms to require disclosure of measureable financial interests or prevent particular types of behavior by investigators, such as fabricating data. And while these policies may have their limitations and sometimes rely on voluntary reporting, they are formalized and they utilize

Page 124

standard enforcement and reporting procedures.

In contrast, these tobacco-specific funding policies don't really cite specific mechanisms to prevent bias or lack of objectivity in research. They are comparatively informal. They don't cite the fine mechanisms for enforcement, but really, they focus on the unresolvable conflict of values as their primary rationale.

So in some sense, their purpose is not so much to regulate research or regulate the conduct of research or how it's governed, but to really make a public statement and put the institution on record on this issue. And it's hard indeed to imagine any circumstances under this sort of policy under which a funding arrangement with the tobacco industry would be acceptable.

So I just wanted to conclude with some issues to consider, I think, going forward in thinking about how we would handle third-party governance of research funded by the tobacco industry. So first is, I think it's important to keep in mind who stands to gain from a particular

Page 125

governance structure or arrangement. I think, as we've seen here in the past, the tobacco industry has gained far more than the public health community from its involvement in public health research programs.

Secondly, conflict of interest and research integrity mechanisms are necessary but not sufficient for addressing the concerns over tobacco-industry funded research. Industry involvement in the less hazardous cigarette program was not a secret, but the industry representatives were still able to have an adverse impact on that research.

Third, I think it's important to be aware of how a tobacco company or companies might use their support of research or contractual arrangements with an independent research institution in ways adverse to public health, such as for PR purposes or trying to use the independent authority of a third-party organization to endorse a certain approach to research or certain conclusions about less hazardous products.

Page 126

Fourth, it's important to think about who defines the research agenda in question. So our concern is not just with making sure that research is conducted in a way that preserves scientific integrity, but also thinking about who decides what are the key research questions and who is involved in that process. Certainly, I think it was, in the case of the less hazardous cigarette program, not beneficial to have industry representatives involved in that role.

In addition to the concerns about the need for independence and transparency, I would add that diversity of disciplines is important, too. This is another lesson that came out of understanding the history of research on low-tar, and light cigarettes, and the less hazardous cigarette effort at the NCI.

Because the research program was defined very narrowly, it was more vulnerable to being misled. And so, for example, there was no research being conducted under the NCI less hazardous cigarette program on smoking behavior or mechanisms

Page 127

of addiction. This was, of course, at a time when addiction, at least in the public health community, was not well understood, so ensuring that kind of diversity of disciplines is important, too.

Finally, I would say that there is a real and potential danger in putting the FDA in the role of approving certain research structures or arrangements, as this creates exactly the kind of semi-official stamp of approval on research conclusions that can be potentially misused as in the past.

So thanks. I'll stop there.

(Applause.)

MS. DILLEY: A couple of questions? Yes?

MR. ROSE: Hi, Jed Rose again. Mark, could you elaborate a little bit on the term – and in previous talk as well -- the term the tobacco industry has used as if it's a monolithic entity, more of a monolithic entity that hasn't changed in the last 50 years?

Just two examples to stimulate your thoughts, whereas decades ago, everybody remembers

Page 128

the image of tobacco company CEOs saying, "Nicotine and tobacco is not addictive," and so forth. And now, some companies explicitly state that smoking is harmful and causes addiction. Some companies have engaged in ethical funding of research.

Also, if, for example, a deregulation were to go into effect that classifies e-cigarettes as tobacco products, then there is suddenly going to be created a raft of companies which will now be part of the tobacco industry.

So I guess what I'm suggesting is there's tremendous heterogeneity within the present and probably future tobacco industry. So to continue using the label "the tobacco industry" doesn't seem to be accurate anymore. And while we should all remember the past and learn from it, what do you think about how do you learn about the evolving future of companies that may be making products virtually indistinguishable from NRT?

DR. PARASCANDOLA: Yes. I think that's an important point. I used the term tobacco industry here in part because I was talking about an

Page 129

organized strategy that was being put forward through the Tobacco Institute, which was representing the leading tobacco companies at the time. So I think it's fair to call that organization representative of the tobacco industry.

So in the episodes I'm talking about during the '60s and '70s, when research was being conducted on low-tar and light cigarettes, I think it's very accurate to refer to the tobacco industry in this combined sense.

I wanted to draw some lessons that are still relevant I think today. What we can learn from the past is that even if the Tobacco Institute no longer exists, some of the same strategies that had been used by tobacco companies and the tobacco industry as a whole are still of concern today. So I think the lessons still apply, whether we're talking about the tobacco industry as a whole or certain individual companies.

So, yes. I think that was the point I wanted to get across here.

Page 130

MS. DILLEY: Other questions?

(No response.)

MS. DILLEY: Great. You'll be back up for the Q&A after lunch. So thank you very much.

Next, the last presenter for this panel is Eric Donny, who is an associate professor of psychology and psychiatry at the University of Pittsburgh.

Presentation – Eric Donny

DR. DONNY: Good morning. So by way of background, I'm a researcher that does work on nicotine, the role of nicotine and other constituents, and drug-associated stimuli on reinforcement and dependence. I am particularly interested in how those mechanisms lead to the consequent harm of cigarettes. This work is an NIH-funded project, and the goal of that center being to determine how market reduction in the nicotine content of cigarettes might be used to impact public health and to improve the health of current cigarette smokers.

So I come to this from a very practical

Page 131

perspective. I'm in the trenches, so to speak, and so I'm going to take a practical perspective on this question. I feel like much of the discussion so far this morning is -- and it's appropriate, but is at a very high level. To some extent, the details are going to matter most here. And so I'm going to spend a little bit of time on those.

So my perspective on this issue that we're discussing today is that the current situation in which the most addictive and deadly project is also the most widely used is entirely unacceptable. And I've been in this field, believe it or not, for over 20 years, and I find it appalling, to some extent, that we still have this conversation.

So with that background, I also view the Tobacco Control Act as giving the FDA the power to effect important changes with the potential to greatly reduce the death and disease caused by tobacco. This potential, however, cannot be realized without the active participation of researchers like myself. And I'm speaking today with my own opinion. I'm not trying to represent

Page 132

all researchers. But certainly I think some of the issues I'll talk about today are those that would be held by other colleagues.

So whatever systems develop for assessing modified-risk tobacco products, researchers have to buy into that system. If they don't participate, it won't work, and there will be no action taken for modified-risk tobacco products, and potentially, continued harm will persist.

So hence, the priority for me and, I hope, for CTP, is to find a way to get this research done and to do so in the most efficient manner possible. Regulation invariably slows progress, and that's okay here. I mean, it's a necessary evil for many of the reasons that have been talked about today. However, unnecessary barriers and inefficiencies in a system of products that could truly be modified risk and therefore could improve the health of thousands of Americans, have to be overcome.

So this research has to be independent, but it also has to be unbiased, and robust, and able to withstand scrutiny to allow FDA to act swiftly.

Page 133

So although our focus today is modified-risk tobacco products, I think we need to be cognizant that there's really two types of research related to products that could be impacted by this model. And this was alluded to a little bit earlier.

I want to keep the focus on modified-risk products, but the other path for reducing the death and disease caused by cigarettes is through product standards. And it's unclear to me whether or not a third-party governance model might have some influence over this process as well. So I think it's important that we keep in mind this other process.

So from a practical perspective, what do researchers need? What do we need to do? What do we need to have in place to do our work? And here's just a list of a few of the things I'm going to cover.

So starting with funding -- I don't want to spend much time on this. I think it's pretty clearly articulated in the IOM report, and also, I think it's something that we probably largely agree

Page 134

on. But to state the obvious, any funding associated with modified-risk products cannot be from the tobacco industry, and institutions have to be assured -- and Joanna touched on this -- that all contracts and grants given to researchers at their institutions are free to report the data and they interpret those data regardless of the outcome. That has to be the starting point.

I'll talk a little bit more about this in a bit, but that assumes that academic institutions are actually the place where this testing occurs. Another model and one that certainly could emerge over time is when it's done through contract research organizations. And so the concerns would be different for CROs than they would necessarily for academic institutions.

I personally think that academic institutions, especially at this point in the development of the science of modified-risk products, are going to play a critical role. Maybe someday in the future, CROs will be able to have the expertise to conduct the work. But the

Page 135

scientific standards aren't clear yet, and so the engagement of academic institutions is going to be important.

In many ways, when I think about the role of the industry -- and I'll use that loosely -- in such a process, I think that it's really in some ways as simple as providing the product, providing the product claims, and the required or requested information about that product to facilitate the independent evaluation of the product.

The third party or the FDA should facilitate appropriate disclosure about the product and be able to evaluate the potential impact of the product constituents and the design characteristics in a way that guides research.

Compared to medications, tobacco products are incredibly complex, with hundreds of constituents and design features that could impact their use and, ultimately, their effect on the user.

So the FDA needs to err on the side of transparency about products, which may come into

Page 136

conflict with proprietary information that the companies want to protect. However, given the history of tobacco products in this country, I think transparency has to win over proprietary information.

Like medication trials, we need appropriate control and comparison products. This isn't obvious how this is going to be done. What is the proper comparison for a modified-risk tobacco product? The identification of design decisions like that is going to need to involve academic researchers.

We'll also need to likely navigate -- and I know this through firsthand experience -- a regulatory environment, investigational product use. And this is one of those parts of the system that could be, if we don't address it directly, an inefficiency that could lead to continued use of more dangerous products instead of less dangerous ones.

Relatedly, I also believe we need a full description of the known risks from hopefully some

Page 137

sort of adverse event tracking system. And this is, I guess, where I imagine a more unifying third party system, not a bunch of splinter systems that actually serve as a fast way for an industry, a particular product to get approved, but a broader adverse event tracking system so that we can understand the relative risks of products. And that can only be done through such a system that we all utilize.

Finally, again, from a very practical perspective, as a researcher who has to go to my IRB and say, "Here's a product I want to study," I need an entity. I need some standards to educate my IRB so that I can go about this research with the highest degree of integrity, but also with some efficiency, that I don't get bogged down in a process that I can't communicate to my IRB, and therefore can't study products that I think might actually have some potential use.

A critical issue that I'm also not clear about is what methods or measures will be used to evaluate products or even whether a standardized

Page 138

approach is actually feasible at this point. If it is the case that the design and data required by the FDA are largely prescribed, then the role of an academic researcher will be diminished, and they won't engage in the process because their institution won't look fondly on that kind of contract research. Indeed, most institutions would have little to do with that sort of process.

So that said, I can imagine the FDA considering evidence from a wide range of methods and measures, some of which are shown here. My personal opinion is that the evaluation of modified-risk tobacco products is so new that standardization is many years away and will be a difficult process to describe.

If that proves true, then, again, the expertise of academic researchers on what design and methods need to be utilized and how to properly evaluate a product will prove critical. It is in those details that the honesty of research is best expressed.

There are other tangible things that I can

Page 139

imagine a third-party system doing. I can imagine, for example, that the entity could reduce the burden of addressing some of those regulatory hurdles. They could facilitate some of the challenges related to the product, things related to the storage, distribution, blinding of product, the choice of comparison products; that we don't want the industry making those decisions because they're critical design decisions that will ultimately impact the interpretation of the data, and the independence of this entity and the researchers will be paramount.

They even can support things like a biomarker analysis or something that allows researchers to do the things that will prove critical in the evaluation of a product.

Relatedly, the third party could provide needed services related to ensuring the quality of the research, study monitoring, and standard for drug development. And I know it's mentioned in the IOM report, or at least quality assurance is. But to date, the FDA has no clear policy about the

Page 140

requirements for clinical trials and the need for study monitoring. And as someone who is in the trenches, I can tell you that I think study monitoring, independent of the researcher and the industry, is going to prove critically important.

Finally, this can't be emphasized enough. Given the deep distrust that we've heard about this morning and that many people have written about, industry and industry-sponsored products have to be evaluated by independent investigators. Any model we consider cannot infringe upon that independence; hence my idea that in some ways, it's relatively simple. Provide us the product and nothing else, information about the product, and let the researchers figure out whether those claims are justified or not.

So in sum, I think the third-party system must serve three things. It must facilitate the researchers' ability to conduct the needed research in an efficient and timely manner. Too many people continue to use the most deadly product and each day of unneeded delay literally costs lives.

Page 141

The system must of course ensure the quality of research procedures and data. It must have checks and balances such as the close monitoring of trials. And finally, the system must protect the researchers' integrity and independence. Without this, it will fail in facilitating the goal of the actual act, which is to improve public health. And that's it.

(Applause.)

MS. DILLEY: We have some time for a couple of questions. Yes?

DR. PETERSON: Nice presentation. Eric Peterson. Duke University. Just curious. Who provides the funding under your model for those researchers to carry out the research?

DR. DONNY: Yes. So are you asking whether it is partly provided by public and partly provided by private or the entity itself?

DR. PETERSON: I just didn't hear.

DR. DONNY: So from my perspective as a researcher, the funding would have to come from an entity that is separate from the industry. So if

Page 142

that third-party entity, for example, grants or contracts, that the institution can recognize as independent of the industry's goals, then I think that's an okay system.

MS. DILLEY: Other questions for Eric?

MR. DOBBINS: I just want to issue -- and this may be just a bit of a challenge. But I think Matt made the point earlier -- and it's one I concur with -- it certainly is clear that you can make a nicotine delivery product that's less hazardous than a cigarette in what probably is the lowest consumer safety bar you can conceive for anything. But it's not clear to me, as you say, that lives are at stake, that the creation and entry of that product into a commercial marketplace where the cigarette is ubiquitous, billions and billions of dollars a year are spent promoting it, and it's sold by an industry that has demonstrated an unceasing dedication to protecting its market share in the cigarette, really that there are lives at stake, as you say. And I wonder why you draw that conclusion.

Page 143

Of course, this goes back to the standard in 911(g)(1), which is a public health standard, and marketing and how the product interacts in the marketplace will be critical.

DR. DONNY: Yes. So I couldn't agree more. And I think that, ultimately, that's the standard by which all products have to be evaluated, is are they more likely than not to provide an increase in the public health, to improve public health?

So I don't disagree with that at all. So I don't want to say a priori that any particular product or any set of products is likely to do that. I simply think that we need to ask that question of all products that are submitted because it is certainly possible that some will.

If that's the case, we need to keep that in mind. We need a true evaluation of that and an efficient one because, in that way, lives are at stake. If you imagine a product that actually could improve the public health, then it seems to me that we have to have a path to get there.

MS. DILLEY: Another question? Ay other

Page 144

questions for Eric? Please introduce yourself.

MR. GRAFF: My name is Don Graff. I work for Celerion. So as someone else who works in the trenches, I really appreciate your presentation. I want to touch on a question, a previous question here, with regard to funding of a third-party entity under your model. Where would that funding ultimately come from?

DR. DONNY: I'm not sure I honestly have an opinion about that, except for to say that, as a researcher, that any funding provided by industry would have to not infringe on the independent evaluation of the product.

So that's the link that has to be broken and broken with much clarity because researchers are very trepidatious about this. They are rightfully scared to engage in this, and so am I. And so in the end, I need to know that whatever source of funding there is, it does not impact -- and my institution will have to know it does not impact anything that I do, my ability to publish the data, and the conclusions that I make about that product.

Page 145

MS. DILLEY: Thank you.
So we have time for one more question. I'm going to break a little early.
MS. LEE: Monica Lee from GTI. One question I think might be better for the agency is, when we talk about research, there's a type of research which would come into a variety of tobacco products, working on the study designs, or you talked about method and measure. I think it's very important, because right now, we do not have that kind of information. There are also studies, or testings, or research specific to a potential MRTP candidate.
So I think as we talk about conduct, it seems like a lot of discussion is geared toward the common type of studies, evidence which may not be tied to a specific product. But at the same time, and I think from the industry perspective, we also need to understand a particular product, how that goes through evidence that FDA may need.
So when we talk about third-party governance, are we talking about type of study

Page 146

designs, structures, evidence-based applicable to all MRTPs, which is big research, or are we here to talk about a product, somebody has an idea, and might have a potential for MRTP, and there are steps that we know we have to go through, for example, through draft guidance, that came out a year ago?
MS. DILLEY: I'm not sure that was a particular question to you, Eric, but I think your point is -- and several speakers have talked to some portion of that -- there is different kinds of research, whether it's specific, as you said, to an application, whether it's broadly applied to MRTPs, or it's even broader than that; and what are we talking about? What governance structures are situated for what types of research, how that governance structure operates, who comprises it, how it's funded.
I mean, there are lots of different dimensions that people put on the table in terms of what -- or some constellation of traits that are either more or less acceptable from people's point

Page 147

of view. And I think that's part of the discussion that people are trying to raise, a variety of issues.
So it's a good point. I mean, I think we haven't been rigorous about talking about one specific type of research, and, in fact, there are lots of different ways third-party governance could be applied. And that's I think part of the discussion, part of the issues that people have raised, and part of what CTP wants to hear more about in terms of providing input and perspectives.
So with that, I want to thank you again, Eric, for your presentation.
(Applause.)
MS. DILLEY: Just a reminder about logistics for this afternoon, one is that we're breaking about 15 minutes early, so you have an hour and 15 minutes, which is good because you have to go hunt and gather for yourselves on food. So I'll give you a little bit more time. There are, again, recommendations, a book out on a table out there.
Then we will start right back up at 1:00

Page 148

with the Q&A from this morning's panel. So we'll start that at 1:00. That'll be an hour and then we'll go into some of the presentations around the models. So thank you, and we'll see you in an hour and 15 minutes.
(Whereupon, at 11:43 a.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N
(1:01 p.m.)
Q&A Session – Abby Dilley

MS. DILLEY: Good afternoon. We're going to get started. And as you know from your agenda, we're coming back to the panel this morning. Daniel Carpenter had to leave, which is why we had a little bit longer Q&A period for him, but he had to catch a flight to Paris, poor guy. Yes.

So he had to leave around lunchtime, but we do have all the members of the panel who spoke prior to lunch up here to address questions. And we will take questions from the audience. And if there are some submitted via e-mail, again, we encourage those of you who are attending online to do so.

We're going to make a slight adjustment to this afternoon's schedule, per the presenter's request, which is, after the Q&A session for this morning's panelists, we'll take just a short break, maybe do our 15-minute break then, and then come back for the full panel discussion of the models

from other arenas.

So Richard Kuntz and Eric Peterson will be here to talk about those models. And then Mark Parascandola, who had been part of the morning's panel, will start trying to draw from those experiences and applying them to tobacco and some of the issues that were raised today. So a little translation of some of that, and some observations, and then also have a Q&A session this afternoon for those panelists to talk about the models.

So with that, I will open it up to the group for questions for this morning's panelists. You also can ask questions of one another if you would like, and we'll get started.

MR. HUFFORD: I'm Michael Hufford from eNicotine Technology. I thought it was a wonderful session this morning. Thank you. One question I had was about the evolving nature of this marketplace and what it means to be a tobacco company, maybe not today, but maybe five years from now, when the modified-risk tobacco product guidance is really off and running, perhaps in a

number of different ways.

So the question tonight for the panelists, just to get your thoughts on this, is if GSK were to make and get approved a nicotine device using organically grown nicotine, but approved through the Centers for Tobacco Products as a modified-risk tobacco product, would GSK be a tobacco company?

If not, why not? And then also, conversely with their existing line of nicotine replacement therapy products, although approved through CDER -- and I appreciate the very different regulatory mechanism -- is GSK a tobacco company? And again, if not, why not?

MS. DILLEY: So part of your question, I think, is linking it back to its relevance for the viability of the third-party governance structure. And so the question is who governs or what role they might have as part of industry.

Is that what you're asking? So anyone want to start? David, yes.

MR. DOBBINS: I have a quick response. I think when you hear people like us, or you hear

me -- I won't speak for everyone else -- say the tobacco industry, what we're really talking about is the industry that's selling deadly tobacco products like cigarettes and high-nitrosamine oral tobacco.

The reason I think you see public health looking at scants of those companies is it's impossible to separate their motivations to obtain market share in those deadly products from their motivations to sell these other products that allegedly are going to show up in the market and make everybody healthy.

The difference with GSK is the product they're selling isn't deadly, and it's designed for a specific therapeutic purpose. And it doesn't face those kind of competing incentives.

So I think what you're hearing when I say tobacco industry, I'm thinking really about cigarettes and high-nitrosamine oral.

MS. DILLEY: Other comments for the panel?

MR. MYERS: It's a more complicated question because of the position taken by the electronic

Page 153

cigarette industry, which was the industry that claimed it was selling a tobacco product. And therefore, it framed from a legal standpoint which category it fell into. It had the opportunity during the evolution of this legislation to be treated differently and to be considered differently. And instead what it chose was first to exempt itself from this legislation and then to fight FDA's effort to treat it as a drug and device.

So in its effort to escape all regulation, the electronic cigarette industry has resulted with a judicial decision, whether we agree with it or not, that now throws it into the category of being a tobacco product. Now, does that make somebody who manufactures it a member of the tobacco industry? I'll leave that definition of game playing to others to decide.

I think what's more important is to take a look -- ask the question about how it should be regulated, what rules should apply to it, how they should be applied, and whether they can be applied

Page 154

in such a way that produces a public health benefit, doesn't just expand dual use of those products combined with all of the other tobacco products that we know kill, with regard to those issues, which is the reason why I think many of us were most concerned about how do we get them into the discussion about how to be regulated and why it is so truly unfortunate that their answer was, "Don't regulate me at all."

MS. DILLEY: Other comments, Eric, or Mark, or Joanna, the question at hand? Is it a complex question around how you define industry and what that means in terms of governance of the products, et cetera? And Matt identified it's a fairly complicated question, but from your perspective.

DR. PARASCANDOLA: I would just add that I would agree with the comment that, really, the issue that -- conflict of interest, I think, that's the key thing here. If a company has a vested interest in an existing tobacco product that they already sell, I think we would view that company differently than a company that is not currently in

Page 155

the tobacco market, however that novel product is categorized.

MS. DILLEY: Joanna or Eric, you're good? Okay.

Other questions? We'll go back here and then up here.

MR. DELMAN: Farrell Delman, TMA. I agree wholeheartedly on the issue of profitability. I don't think anything is going to go anywhere in terms of companies wanting to market products if they can't make money. I think that's a given. And I think, David, you're absolutely right. Profitability is key.

What may be less understood is the fact that the Reynolds CEO, Delen, has said he makes twice the profit on Camel Snus than he makes on Camel cigarettes. He'd love to more Camel Snus. That's low-nitrosamine Camel Snus. If he can get the can down in price, he'd make even more. This is a relatively low economy of scale right now in production because they're not selling all that much. But if they were to sell 50 times as much,

Page 156

he'd make even more. He'd be the happiest camper around if everyone smoking Camel cigarettes moved to Camel Snus, and that's just the dynamic. That's where the profits are for him.

Now, I deal a lot with the new e-cig guys out there, giving them advice on markets and things like that. And my understanding in the e-cigarette business, depending on how they source the liquids, and the flavors, and the complexity there, buy that is a very highly profitable business. That's why we see so many of the players hitting the market now, because even if they're selling small quantities, they're making lots of money.

Now, let's just say for the sake of argument -- since profitability is absolutely key.

MS. DILLEY: Is this to third-party governance?

MR. DELMAN: I want to get to David's point and Mark's point about the connection between profitability, because it's been raised, and any of the issues associated with getting these products out on the market through an MRTP governance

Page 157

process, and what your thoughts are knowing that they are profitable, and they'd be willing to give up cigarettes.

MS. DILLEY: So I think your question is, how much does profitability weigh into it in terms of a governance structure?

MR. DELMAN: No, no. It's just, these companies are willing to give up cigarettes if they were able to promote and grow these other businesses by virtue of being able to make (inaudible – off mic.)

MS. DILLEY: So you're asking about the marketing regulations.

MR. DELMAN: Well, the process of getting the relative-risk claim for a product that is --

MS. DILLEY: I see.

MR. DELMAN: -- known to be less harmful.

MS. DILLEY: I see what you're saying.

I don't know if you've got a question in there on third-party governance or if people want --

MR. MYERS: It's a hard one on third-party

Page 158

governance with regard to it --

MS. DILLEY: Right.

MR. MYERS: -- except that Section 911 gives FDA -- requires FDA to take into account broad public health impact. So Farrell, if hypothetically you were right -- I'm not sure I agree with you about Camel, but that's a separate question. The quotes I've seen from our Reynolds CEO says the money is in combusted cigarettes. But we don't have to debate that. That's not the issue.

The statute mandates that FDA consider what the broad impact of a product's claims will be so that it's either an opportunity or a hurdle for the tobacco company to demonstrate that if allowed to make claims for, in your hypothetical, Camel Snus, and you could really move a substantial number of people off of cigarettes, not just during the eight hours they can't work, then that's a powerful component to be made.

In some respects, the statute has created all the incentives in the world to accomplish

Page 159

exactly the goal you've wanted and to protect, if there's such a thing, the honest manufacturer out there from not having to compete against those who are making either unsubstantiated claims or are engaging in marketing that is really designed to create dual use rather than single use. So the statute creates all the incentives in the world for what you want.

Now, in terms of the third-party independent, this is in fact an area where my view is not controlled by a sponsor or company, where if FDA were funding research or if somebody else was funding research carried out independently, so that there was a way you could trust not just the "product," but how the product was going to be marketed and sold that it would produce that result, then you would get -- and you've got exactly the statutory system that would give you what you want, and a truly independent party would facilitate that.

MS. DILLEY: Any other comments along those lines? David?

Page 160

MR. DOBBINS: Matt, that's terrific and that's a lot better than what I was going to say, which is, the statute sets out the requirements for the exact reasons you say, to make those claims. But why it's relevant to third party -- is the real key here -- is because the marketing of the product will be critical in making the statutory claim.

So if you imagine a third-party entity that says, "If the product looks this way, if it's controlled this way, and if it's marketed this way, it will positively impact the public health. Okay, RJR. Go sell those next to your Camel cigarettes, and we'll step back, and wait, and see if that really happens," I think RJR has to show what it will do. It has to make those claims, and it has to be the one making scientific claims that can be tested, replicated, and analyzed by publicly available data. And that's one of the main reasons Legacy opposes IOM Recommendation 10.

MS. DILLEY: So we have one brief follow-up because we have a couple of other presenters.

MR. DELMAN: I would agree, Matt, that 911

Page 161

sets out a whole range of requirements, and standards, and issues. And obviously, any company coming and making a claim is going to have meet those hurdles.

What it does not do is answer what would be a non-evidentiary, non-scientific claim, dealing with what is indeed the calculus to evaluate population risk. When you look at a product, the new product coming on the market, the concern, justifiably, is non-consumers of any nicotine products at all being drawn to that product versus the individual benefit that would come.

But what is that formula? What is that calculus? What does it look like? Somebody is going to try to meet that standard that is set out, there and you don't know what the calculus is. How could you possibly invest the money to try to accomplish something so unknown?

MR. MYERS: Well, no, it's an interesting question and it's an important question. The statute sets out pretty clearly the criteria. The details from which a formula would come shouldn't

Page 162

be in a statute and are, of necessity, not in this statute. So between FDA, or between an independent panel, or between TPSAC, there needs to be put meat on those bones with regard to that.

I should say to you, perhaps ironically, if the concerns you raise are in fact the concerns of the broader industry, then the fact that a number of manufacturers have challenged the very existence of the public health standard as being unconstitutional, and the fact that the industry has given every impression that if FDA were to try to put parameters on how it was marketed, that that would be challenged under First Amendment purposes, means that in some respects the industry has already -- at least categories of the industry are working against the exact goal that you're talking about, because an agency, in order to carry out that purpose, needs to know that it's working with somebody, an entity, where it can have a role in dictating not only the product itself, but how the product is used. And if you can't be certain about that, then the cautionary principal in the statute

Page 163

says it's got to be careful.

MS. DILLEY: So okay. Mark, you want to respond to that as well?

DR. PARASCANDOLA: Yes. I was going to add, too, that I think in terms of that calculus for evaluating risks and benefits, I mean, if you look at the way the pharmaceutical industry has been regulated by FDA, it has taken us a hundred years to flesh out the requirements for evaluating the risk-benefit calculus for pharmaceuticals, and it's still evolving.

So I don't envision that necessarily an agency would be expected to put in place, in a short time frame, a detailed set of criteria for meeting that calculus. I think it's likely something that would evolve with input from the scientific community and in ongoing research.

MS. DILLEY: So you think that clarity will be developed over time as opposed to that being some role that a third-party governance structure could provide some insight to.

Matt, I think you raised that it could be

Page 164

TPSAC. It could be any number of ways that you would go at that.

MR. MYERS: And that would be an interesting use, broadly answering the question rather than in regard to a specific thing, but to provide those sorts of parameters and thinking on it. I think you won't be surprised. I mean, those of us think it should be done very much independent of the industry so that there is no conflict, so that one can be certain that the people chosen have only reducing the death and disease caused by tobacco products as their criteria.

MS. DILLEY: Right. And that's where it sounds like from concerns raised earlier this morning about it's not for a particular product, but it's for a -- it's giving some clarity around those standards, how to interpret those standards, and what studies could meet those standards.

MR. MYERS: That would be my view.

MS. DILLEY: I know we had a question back here. And please introduce yourself, if you would.

MR. WILLIAMS: Yes. I'm Linc Williams from

Page 165

AEMSA. So there's been a lot of talk about lies and deceits over the past multiple decades. So my question to you is, there are now electronic cigarette manufacturers, hundreds, if not thousands of them, out there. Do you believe that they will perpetrate the same lies and deceits that the tobacco industry did in the last 20 to 30 years?

MS. DILLEY: And it's relevance for third-party governance in terms of their participation?

MR. WILLIAMS: Because I believe -- should the third-party governance also apply to the electronic cigarettes?

MS. DILLEY: To e-cig. Okay. That was the question.

MR. MYERS: I don't think it should depend on anyone's beliefs. I think the purpose of giving the FDA this sort of authority was so that we don't have to depend upon that kind of faith. The FDA should set up a set of rules and regulations that apply across the board. It should be applied even-handedly and rigorously, and that those who play by the rules can benefit, and those who don't won't be

Page 166

allowed to get away with it with regard to those issues.

I think the one lesson of the last 50 years is that until there is a regulatory agency overseeing the actions of companies in this field, that we shouldn't just assume that what they're doing is in the public health's interest.

MS. DILLEY: So it's less of who's doing the research, but it's more what kind of research they're doing and meeting the same standards.

Corinne, you had a question?

MS. HUSTEN: Corinne Husten, FDA. I wanted to ask a bit of a clarifying question because it seemed like the perspectives of the various presenters, in a way, depended on how they were thinking about that term "pre-approved institution." So I was hearing a lot of concern about a pre-approved institution that, basically, a company might set up as their independent institution that they would run funding through, that it might be good on the route of like CAR or some of those.

Page 167

I heard discomfort around sort of just them saying, "Harvard's a reputable institution. Duke's a reputable institution. And the industry can fund researchers from those types of institutions," and that would be a pre-approved institution.

Then I heard what John was talking about was more of an institution that's set up independently and funded specifically for the purpose of doing the grant-making almost in review process, for -- for example, if a tobacco industry wanted to sponsor a product, they could say they needed these types of studies to meet the criteria, the MRTP. And this other institution would then put out calls for proposals, review them, and put out the grant money.

So I guess I wanted to ask, especially Matt and David or the folks who are saying no third-party governance, are you opposed to all models, or what do you see as the potential pitfalls of what Joanna was specifically proposing?

MS. DILLEY: So Corinne, just so I understand the question now, it seems to revolve

Page 168

particularly around the pre-approval concept and then also what exactly that entity is reviewing or governing.

MS. HUSTEN: Yes. Like I said, it seemed like the different sort of perspectives, to some extent, hinged on different sort of definitions of what that pre-approved institution might be. And so I was just curious of how one model was put out there by John. I was just interested in hearing what the other panelists thought about that model specifically.

MR. DOBBINS: I think that there are two questions being asked. And I'm going to set to the side the issue of a third-party entity that does this specific kind of product research for MRTPs. But let's conceive of a situation where you wanted to fund general research to understand the effects of tobacco products, generally, and answer some of these questions, like what are the criteria that you would use to determine the public health standard.

Well, one way you could do that is you could

Page 169

set up a government regulatory agency, require the tobacco companies to pay a certain part of their money into that agency, and then empower the agency to set up and fund studies that would address those questions. But the good news is, we already did that, and it's called the FDA, and they are doing that stuff.

So that, I am fully for. And I must say, those of you who know who I am, I'm from Legacy. And what happened is, the states sued the tobacco industry for the costs incurred through industry fraud that resulted in Medicaid expenditures. They set aside a portion of that recovery from the settlement to fund us. We do tobacco education. And I can assure you that the tobacco industry has no control over what we're doing.

So there are models that you could do that kind of general research on. The problem is when you get into product-specific research and particularly these kind of products, trying to practically apply the model that I think is being advocated here. It just breaks down when you try

Page 170

to apply it in the real world.

The FDA finds an entity, and I'll call it Good Research, Inc. And Good Research, Inc., for some reason, we can trust to do this product research. So Good Research, Inc. takes the new nicotine spray, and says it's great, and says, "If you market it with these very specific restrictions, we think they are great studies that we've done ourselves, that would show that it would reduce public health. Here you go, tobacco industry. You can sell this right next to your billions and billions of dollar market in combustible cigarettes."

Do you have any faith that those marketing restrictions will hold up over time, that the industry can be trusted to do the things that will actually reduce that market? And the answer is, of course you can't. So that's why it just doesn't make any sense to us.

MS. DILLEY: For product-specific?

MR. DOBBINS: Yes. Product-specific.

MR. MYERS: Corinne, let me just try to

Page 171

quickly -- what I submitted looked at a number of other instances where we've tried to do that. I mean, Mark spoke about the NCI Tobacco Working Group. When I was at the Federal Trade Commission, we looked at the impact of the industry funding of the American Medical Association, theoretically, to do totally independent research.

There was the Damon Runyon Foundation, which was set up as theoretically a public institution that was incorruptible to fund this sort of research. And then, of course, you have the litany of the universities that took tobacco money, only some of which we take off this morning.

Then, when you take a look at what they produced, which you found was that the funding controlled the agenda and moved the agenda away from the things that would have a major public impact, that much of the research itself was research that the industry knew in advance would either produce nothing or would run contrary to the consensus that was out there. So that what the lesson for me on those things is that the AMA and

Page 172

NCI are extraordinary institutions, but the money corrupted and the money created an agenda that wasn't the appropriate agenda.

If what you're talking about here is having a third-party entity that isn't designed to help company X move product Y to market, but is designed to help the FDA say what kind of research do we need to do to make sure that products in this category are in fact less dangerous or that marketing of this sort won't produce the results that we're concerned about, that raises a very different set of questions.

But when Dan Carpenter presented this morning, he started off by saying what they were talking about. And he said, "We're flexible. It isn't in the long term what we want. What we're talking about is in fact a sponsor, company X, who has product Y, who wants to move it through the process, and therefore wants you to do research of that sort alone."

There's another question, too, which is, it might not be inappropriate for some third party to

Page 173

help the agency -- although I think TPSAC could do this -- is, say, if somebody is producing a product which they claim causes less cancer because it has lower levels of nitrosamines in it, generically, what kind of research do we need to do to be comfortable with that, as opposed to in the context of, I've got this product out here with regard to it; something along those lines.

But I think the second you get to that other area, you've got a real problem. And I think the notion that it's an independent entity, one needs to be very cautious and skeptical. History just tells us that there are real problems.

MS. DILLEY: Joanna?

DR. COHEN: So we have the FDA, and the Act, and that's great, and it requires research to be done on these products. And I think, as Eric mentioned, a lot of scientists are very nervous about taking money directly from tobacco companies. And I think that's where -- whether this governance structure, again, where there's one, would be helpful to get the best people doing that possible

Page 174

to do that research. Otherwise, what we're going to end up with is the favorite people, contract people, doing the research, and no one is going to be able to trust. Their credibility throughout the process is going to be lost.

So I think we have to think about how we can structure the money through a way, and whether FDA is that third-party governance structure, meeting some of the criteria that we laid out, that could possibly be; we have to think that through. But I think we want to be able to let our colleagues do the good research that's needed in a way that their reputations don't get tarnished and they can continue to do that.

So as I mentioned in my presentation, the one challenge -- or the one criteria that we laid out was the idea of an independent research agenda. And that does completely fall apart when we're talking about MRTPs because, obviously, the research agenda is right there. So that one certainly does fall apart.

MS. DILLEY: Mark and then Eric.

Page 175

DR. PARASCANDOLA: Yes. I just wanted to add, briefly, too, in response to Corinne's question. So I think part of the concern with the notion of -- or the term pre-approval is that the concern is not just with organizations that have been established by industry to support research like the Council for Tobacco Research and that, but also even how the tobacco industry has used the reputation of NCI, of Harvard University, others to sort of aid their corporate image and to provide a semi-official support for their effort to market low-tar cigarettes in the '70s. So that was the historical example I had wanted to highlight.

So even when we're talking about an institution that is independent of the tobacco industry, I think there are still concerns about how the authority of that institution can be misused.

MS. HUSTEN: So I guess my question is -- I'm sorry.

MS. DILLEY: Can we have Eric speak to it? And then we'll come back to you.

Page 176

DR. DONNY: Sure. So, I mean, I guess my assumption is that the only model worth even discussing is one in which the entity is probably more like Joanna laid out, in that if we're talking about a bunch of splinter entities that basically serve the proxy function of being the industry's representative, then of course that's not independent research, and that's not viable, and would not be acceptable to me or anyone else. So I do think that it's more along those lines; at least, that's my opinion.

I think the part that Matt laid out, which I think is where it gets more and more complex, is if you lay out the marketing strategies now for those products and you start to think about how are they actually going to be used in the marketplace and what are we testing in trials versus what are we actually observing post-market in a surveillance system where we think, oh, no, we got it wrong.

I think that's where all the bias and lack of independence is particularly problematic. And I think that's where the FDA or CTP needs to provide

Page 177

some guidance as to what exactly are the questions that this entity and then the researchers who would actually do the work, what exactly are the questions that they're asking. What's the context in which this product is being evaluated? Otherwise, what I think we end up generating is still research that's not relevant to what we're trying to predict, which is how it functions in the marketplace.

MS. DILLEY: And doesn't the statute speak to that in terms of their requirements around post-marketed surveillance and the ability of FDA to pull from the market --

DR. DONNY: Yes.

MS. DILLEY: -- so that we need those anticipated public health benefits?

DR. DONNY: Yes. So my assumption is that any third-party governance model will include both pre-market and post-market surveillance in terms of evaluating the product. Now, maybe that's wrong. I mean, I think that was just my assumption coming in. But I can't see how you can functionally

Page 178

separate the two very effectively.

MS. DILLEY: Corinne, you wanted to follow up?

MS. HUSTEN: Yes. I just wanted to follow up a little bit, especially because what I was hearing is like this set-up would be okay for more generalized research but not for product-specific research.

So setting aside whether you believe there can be a modified-risk tobacco product or not, how could someone potentially bring a product to the testing to bring an application forward to FDA? If the industry can't be trusted to do it themselves, and if there's no third-party governance system that will work, how can there be product-specific research to even bring a product before FDA?

So I'm just curious how you would see a system being developed that would allow for that research.

MS. DILLEY: So Daniel gave a specific example of --

MS. HUSTEN: For a specific product, not the

Page 179

general --

MS. DILLEY: -- like vulnerable populations or -- but that's the example he used; what would that look like.

MS. HUSTEN: Well, I heard a distinction between general research on how you would do studies from product-specific to bring a product to market. So I guess my question is, how would you set up a system to do the testing if someone wanted to try to bring a product to market under an MRTP?

MS. DILLEY: Okay. And then Jed and Justine back here. Anybody want to respond to that?

MR. MYERS: Three quick answers for you, I think. As you struggle with the proper role here, one is I think it's important for FDA to be setting the agenda based on what it deems to be the most important things and not to do it looking at Section 911 in isolation with regard to that.

So in setting your priorities, I think the agency needs to do that and determine with its own funding research, and it has a very substantial budget for research. Whether those dollars are

Page 180

best spent looking at those specific items or whether they're spent looking at other items, I don't want to prejudge that for you.

Second, ultimately, the agency is going to have to evaluate whatever research done by whoever it's done independently. So if I was going to tell you what's your top priority -- my recommendation for your top priority is, in fact, for the agency to figure out what kind of studies it really needs, with what kind of rigor and what kind of methodology, so that it's not at the whim of the industry or "some third party" who the industry is dealing with.

Is that a challenge? Yes. But it was a challenge for the FDA when they took on pharmaceuticals, and it's a challenge when they took on cosmetics, and it was a challenge -- it is. And there's a learning curve because the industry has hidden the information from us for all these years, and so it's not surprising.

But I think that -- because ultimately the agency has to make those determinations. From my

Page 181

point of view, that's where the priority really needs to be at the present time in setting your priorities as to what you do with regard to this. And that way, whether research comes in from a tobacco company, from a university, or from some other third party, you've got the criteria, you have the in-house capacity to evaluate it, and you're not dependent upon subcontracting that out to somebody else. I mean, that was the reason for having such a large budget for this agency, to give it the capability of doing that moving forward.

MS. DILLEY: Mark, did you want to comment?

DR. PARASCANDOLA: Yes. So, yes, it's true. Tobacco companies and especially a new company that's maybe a smaller company may lack the capacity now to do the kinds of studies that are needed. But I wouldn't see them as somehow disadvantaged because of that, because they have the ability to develop the capacity that's -- or they should be expected to develop the capacity they need if they want to market that product.

So I guess, yes, I would agree with Matt

Page 182

that the focus really should be on looking at what should the scientific criteria be to evaluate these products and not primarily on how private companies are going to develop the capacity to do that research.

MS. DILLEY: Any other comments on this particular question here?

DR. DONNY: I guess I just want to clarify that. I would be personally uncomfortable -- and I think based on scientific reasons -- to trust the research that's generated by an industry that can turn profit on that research. Now, that's in part why I think ultimately this comes down to a test of independence. The product has to be independently evaluated. And what I mean by that is true independence, separation of product and research.

So I think that that, to me, whether it's in a third-party model or anything else, has to be the criterion in which we develop infrastructure to look at these products.

MS. DILLEY: So research is completely separate from the industry that is making the

Page 183

application.

DR. DONNY: Yes. When I think about the history of the industry, that's what I would emphasize, is there's really -- it's hard for me to imagine any situation where I would be able to trust the research being generated by an industry that can turn profit based on that research.

That doesn't necessarily mean that profit is a bad thing. I mean, obviously, as it's been said, that's part of what will drive innovation. But in the end, that research has to be able to withstand an incredible amount of scrutiny from the public health community, and that's appropriate. And I'm not sure you can reach that goal any other way.

MS. DILLEY: So does that require a separate verification process of researchers in an industry or just they don't even do the research on a new product at all?

DR. DONNY: I mean, this is where I think there's a role for another entity or maybe it's within the FDA. I don't know. But in the end, I think what has to be done is there has to be an

Page 184

independent entity that actually determines whether that research is of value or not. And that is in the details. It's not just in the report.

MS. DILLEY: I believe, Jed, you were next and then Justine.

MR. ROSE: Yes. Eric, you used the term and others on the panel used the term that the history of the industry or history of research supported by the industry. I think it's important to remember that, again, history evolves with time and there's old history, recent history.

I think some of the recent history may be relatively ignored in the discussions. Again, I hold up the example when our institution accepted a tobacco industry grant from Philip Morris U.S.A. And the letter of agreement was posted on our website, and the provisions of that public transparent agreement involved no control by the industry. Ownership of data, publication rights, intellectual property all resided in the university.

As you know, Eric, at any university these

Page 185

days, all of the research we do, whether it's tobacco industry-funded or NIH funded, is overseen by a variety of committees within the university. There is the Institutional Review Board that's been spoken about often. There is the research integrity office that requires conflict of interest disclosures and can prohibit research where a perceived conflict exists. There's a data safety monitoring board in many cases, which we have with our own center, which is another independent set of people who can oversee side effects, and risks of trials, and data management, data quality.

So there's already quite a few oversights within any top-notch academic institution and more coming all the time. I mean, there are new committees being formed for new oversights all the time. And so I just wonder how many -- and many more oversight is needed for certain to protect against specific concerns.

But I guess what I would invite you or ask, why isn't there more interest in really delving into learning about the current history of how

Page 186

things are done rather than focusing solely on the relatively ancient history? In fact, anyone who wants would have an open invitation to come and get a seminar on what we have accomplished in terms of advancing smoking cessation science with tobacco funding that we've done, and what our oversight mechanisms and mechanisms for protecting the integrity of the research are.

So when you off-handedly dismiss all academic research as being under the control of the industry, if that's where the dollars come from, I think that's not true. There could be a lot of oversights in place that do protect the integrity of the research.

MS. DILLEY: So maybe another way to frame it, too, is, are there governance structures already starting to evolve at academic institutions or anywhere else that are meeting some of the criteria that have been discussed, that would make them more or less viable?

I think, Joanna, you had put up some criteria. Others had mentioned other kinds of

Page 187

criteria. So, Eric, I don't know if you wanted to answer, directed it to you, and anybody else can chime in.

DR. DONNY: Sure, Jed. So I don't disagree with many of the things that you said, that there are -- and I certainly am sympathetic to the number of regulatory things that we have to jump through to prove that our work is of the highest integrity. So I agree with that.

But I think the practical reality is that whether you take recent history or a longer view of history, the level of skepticism is incredibly high, whether you think it's justified or not. And without passing judgment on whether it's justified or not, I think my colleagues would be happy to probably contribute to that. But in the end, practically speaking, I don't think the work moves forward unless the system addresses that level of skepticism.

So while I understand what you're saying, I think that there is no way to assure the vast majority of researchers of their independence and

Page 188

their contribution to an independent evaluation of a product that they, as tobacco health -- or as public health servants, that they can do their work and actually be viewed as having a high level of integrity and independence. I think it's just a reality of the playing field right now, and I think it's difficult to view it any other way.

MS. DILLEY: Joanna, your criteria were exactly for that, and I think you've emphasized that the interest is meeting those criteria in some way to protect the integrity of researchers at institutions.

So I don't know if you want to speak to that anymore in terms of what kind of models you see emerging out there or, again, some more discussion around how structures could meet those criteria.

DR. COHEN: Well, I think we're talking about other models shortly.

MS. DILLEY: Yes.

DR. COHEN: What I see in reality -- I mean, there's Jed, there's you, who's taking tobacco money. There are a couple of other people, other

Page 189

respected researchers who have. But the vast majority of people that I have talked to are not willing to do that because they're just not ready to do that.

So that's fine. Actually, if you don't mind, maybe I'll ask you what you see as an effective governance structure for MRTPs.

MR. ROSE: First, can I just follow up both on what Eric said and your follow-up? What I'm hearing is that, whereas it may be possible to conduct high-integrity research with sufficient oversight, the fact that people believe that it's not going to happen is what should dictate the system, which, I mean, I could think of analogies of that.

But it's sort of like one could think of distasteful events in the history of America where there may be no reason not to associate with certain people, but since everybody thinks you shouldn't associate with certain people, then we have to preserve the fact that we shouldn't associate with certain people, whether it's due to

Page 190

color, or political beliefs, or whatever else.

So I think we have to get beyond perception to reality, even though many conflict of interest committees do say that the appearance of conflict of interest is important as well as the substance of the conflict of interest. But I think that the emphasis should be on substance rather than superficial appearances.

So in that sense, the fact that many people don't feel comfortable accepting tobacco industry funding is simply because of the groupthink pressure that has been exerted by very vocal members of the tobacco control community that tried to say it's the wrong thing to do, as opposed to saying that it's the wrong thing to do if it's not independent, if it's not of high integrity.

So if something can be done with oversight that guarantees the strong likelihood of integrity, at least as much as I'd say with the pharmaceutical industry-sponsored trials, then I think we have to go beyond the belief that it's impossible because everybody has said it often doesn't happen, and see

Page 191

what is possible and how to make that happen.

In terms of what I think is the ideal oversight, I actually don't have a strong opinion. I'm speaking up for the strength of academic institutions just because I hear that being given short thrift and unfairly so. But that doesn't mean I think that's the best or the only way to move it forward.

But coming back to Eric's phrase "swift and efficient," whether it's 448,000 people dying every year or what the current figure is, we do have to think of swiftness and efficiency. And if it's possible to utilize existing oversight to rapidly carry products forward that might save millions of lives ultimately, then I think that has a certain advantage over taking what might be years to set up yet another oversight entity.

MR. MYERS: Can I just jump in? Just a quick thing. One is, we're not talking about ancient history, Jed. Judge Kessler found that this was going on as the case was heard, the case was being tried. And she found that given the

Page 192

tobacco industry, the companies that were before her, that there was substantial reason to believe that it would continue to go on. And I think that's important.

Second, I think all of us have said that whether it's a university, the FDA, or an independent entity, what's absolutely critical is that there be a set of criteria. And Joanna laid out ones that there are pretty broad consensus behind, that absolutely guarantees the integrity of what's going on, but that includes integrity of agenda setting, which industry research has never allowed before. They have funded research to accomplish what they wanted to accomplish, not what was really in the broad public health.

Then the third thing you do have to deal with that goes over and above that issue, which is an issue with any funded research, but becomes more of an issue with companies who have the history, recent as well as past, that the others do, which is, you want your next research grant.

So it's one thing to have that concern when

Page 193

you don't either have the history or the kind of product you've got here. One has to think about how you build the barrier so that the desire for the next research grant doesn't -- despite all the rules and regulations, despite the integrity of the researcher -- implicitly bias the system.

So it is more complicated. But I don't think there's a single one of us who have said that the concept of independent research, per se, is a bad idea where the researchers set the agenda, where there is a break in the link between the companies and the research that's being done, where the researcher owns the data, where the researcher doesn't have to produce results that the company likes in order to be sure to get their next research grant.

So I think you've misstated what's out there, and this is not groupthink. The tobacco industry is having trouble finding people to take their money because of what they've done, not because of what people think.

MR. DOBBINS: I just want to add something.

Page 194

It's not only what they've done. It's what they're doing. Keep in mind 430,000 plus people are still dying of the product they're selling and half the people that use it die. And ultimately, many people, researchers and institutions, decided that is sufficient to not take the money that results from that blood.

So I also concur with Matt, and you won't hear me say anything different. The proof of the pudding, the integrity of the research, will be in the ability to replicate it, the ability to look at the data, and I also concur the FDA developing the expertise internally or through contractors beholden to the FDA to evaluate the evidence it's presented.

MS. DILLEY: So we've had a couple of comments. I mean, we could do this all day. I'd really like to get to a couple others. I want to go to Justine and, if we have time, come back, or you can ask it at the break.

Justine, could you introduce yourself?

MS. WILLIAMSON: Justine Williamson from

Page 195

British American Tobacco. I would just kind of like to ask the panel to expand a little bit on their definition of independent. I came from the SRNT conference last week, and this is the first time we're starting to hear data that e-cigarettes may be cannibalizing the NRT market. And then, obviously, that's making NRT and e-cigarettes competitive products. And then we're talking about fighting for profits.

So would an organization or an individual that takes money from PhRMA then still be truly independent?

MS. DILLEY: Just for the people online NRTs are nicotine replacement therapies. Right? I'm just trying to interpret some of the acronyms. So the question to the panel, a little bit more on independence.

MR. DOBBINS: I would just actually go to you, Joanna, the paper that was written really does set forth a criteria of independence. And from my point of view, primarily, what you want to see if there are dollars that are flowing from the

Page 196

industry -- and I think Matt phrased it as a complete break -- you want a complete break of governance and agenda-setting. And historically, in order to get that, what in actuality happens is that the industry has to be forced under duress to give up the money because they don't want to do that, which is why the Legacy model worked. The states took the money from the industry recovering from the injury that was done through the tobacco industry fraud. And it was the state's decision to give the money to the Legacy Foundation to conduct a truly independent agenda.

I think any -- and this is why I pointed to the FDA as a model of why I would do that. The FDA isn't beholden to the tobacco industry. The FDA is beholden to the political controls, and any agency is. And they should be making the decision about what the research agenda is, not some heretofore unknown third-party entity that's serving the interest of getting commercial product to market.

MS. DILLEY: Let's take Joanna's comment and then we'll have time for one more question.

Page 197

DR. COHEN: For what it's worth, I think whatever governance structure is created, it would apply to traditional tobacco companies and other companies for the type of research that's being done.

MS. DILLEY: We've got one more question here, and then we'll take a break.

MR. MOYNIHAN: Well, there have been a lot of attempts to kind of broaden the discussion about third-party governance and industry-sponsored research, but in the case of modified-risk tobacco products, the agenda is kind of set. The question is the goal of how do you have a system that gives people confidence in the data that is being presented in support of the modified-risk tobacco product applications. That's really the question that I'd like to hear a more direct comment about, rather than all of the other areas of tobacco research.

MS. DILLEY: So you are asking specific to modified-risk tobacco products, for third-party governance? Eric? Question?

Page 198

DR. DONNY: We weren't positive what the question was, so, Mike, if you could clarify.

MS. DILLEY: Okay. Can you repeat it? It sounds like -- we've been talking about third-party governance for a range of different kinds of research, and you're asking specific for MRTPs.

MR. MOYNIHAN: Right. The question of agenda setting -- the agenda -- the question -- the agenda is, we have a structure, a formula, and some guidance about applications for modified-risk tobacco product applications. We have some skepticism about why anybody would file those applications and whether the data can be relied on.

So we have a very specific agenda in that sense. And the question is, is third-party governance applicable to that situation in a way that's different from these broader questions? In my own opinion, for example, academic research, there's really nothing publishable necessarily from the third modified-risk tobacco product application, for example.

MS. DILLEY: So is there anything inherently

Page 199

unique about MRTPs that shape a third-party governance structure? Yes?

DR. PARASCANDOLA: I'm just saying -- and I think it was commented before that different arenas of research and data collection may require different structures. I mean, obviously, they all need to meet certain criteria in terms of independence and integrity, but it's not clear that the same arrangement will be applicable for all situations. And I think -- so, yes. I would just add that.

MS. DILLEY: Any other comments on that?

(No response.)

MS. DILLEY: All right. So we would like to take a break now. We'll take the 15-minute break, so we'll start back up at 2:15, and we're planning to go through all the presentations on models. So we have two models and then some discussion about linking lessons learned to tobacco. So we'll start right back up at 2:15.

(Whereupon, a brief recess was taken.)

MS. DILLEY: People, let's take our seats

Page 200

and we'll get started.

So just a couple of brief comments about this afternoon's session. As you heard Daniel Carpenter's presentation this morning, IOM sent out a couple of examples just for food for thought. And we have two speakers this afternoon to talk about their experiences, and some models and work that they're doing in terms of looking at some of the issues around governance and of research.

Our first presenter will follow somewhat the same structure in terms of we have two presenters to talk about those. And then Mark Parascandola will make some observations about these models and their relevance to tobacco-related research. And then we'll have an hour for Q&A again this afternoon, after those three comments.

So first up, we have Richard Kuntz, who is senior vice president and chief scientific research and regulatory officer at Medtronic. So I'll turn it over to you.

Presentation – Richard Kuntz

DR. KUNTZ: Thanks. Good afternoon. Before

Page 201

I talk about the experiences we've had with mainly a data-sharing experience in trying to shape how to make data more transparent in the process and more transparent in the medical device arena, in speaking with the next speaker, Eric, we thought we might just give it a very quick kind of overview about how devices and drugs work.

Our company, Medtronic, spends about $450 million a year on research, and it's 100 percent controlled by Medtronic. So we do our own research; that is, we decide to either do it in house or contract with CROs to do this stuff. And the protocols for maybe between 300 and 400 products per year we're studying at any one time are very highly regulated by the Food and Drug Administration.

The studies are followed very carefully. And if the studies are positive, we go to the next level of product approval. If they're negative, we don't. And so we had a handful of negative products and history, where we found out the product doesn't work to the standards that were

Page 202

established by the FDA, and those products don't go forward. And then the ones that do, we do go forward.

About half of the studies that we do are also post-market studies, looking at the expansion of an existing label or uses outside the initial intention with intent to go back and get a re-label. Those studies are also generated by our company to go forward.

So it's a model which inherently doesn't have a sense of independence with a third party overseeing that. And that would be a large resource requirement, to get third parties to actually look at all drug and device companies, because virtually all companies work that way.

So I'm going to go through an experience we had, where we're actually trying to push the envelope on data transparency.

We sell a product called Infuse, which is a bone morphogenetic protein, and it's made by Wyeth. And it was introduced into the market around 2001. And it's used to help the advancement of

Page 203

osteoblasts in bone, to fuse bones, mainly in spine operations. So when you have degenerative joint in the lumbar space and you have to have the disc removed, the spine become unstable. It has to be fused to the vertebrae above or below it. And it's usually done by a combination of hardware that's put in by the orthopedic surgeon or surgeon and also fusion.

The standard has been to graft bone from the iliac crest in the pelvis and transfer that into a cage, and that's been used for 30 or 40 years. And we introduced a product that actually would not require you to do the harvest of the bone and potentially has the same or higher efficacy in actually causing fusion.

In 2002, there were four or five randomized controlled studies that led to its approval. There's a panel that reviewed it. And then there are about five or six studies done subsequently over the ensuing years, the last one about 2010.

The indications were very straightforward for one level of anterolateral lumbar interbody

Page 204

fusion or ALIF. Based on the evidence, the FDA approved the product. And peer-reviewed publications, which is another layer of a way to communicate, is mainly how the dissemination of the information gets to physicians.

So think of a couple spheres of data. There's data, which is all the data, all the studies we do, individual patient-level data, and then there's data that gets condensed and are necessarily subsets, which are peer-reviewed publications written by independent physicians published in an independent process called peer review.

So most of these peer-reviewed publications are specifically focused on certain topics. None of them ever look at the entire data set as a whole, and that's generally how medical products are approved.

In June of 2011, a major challenge was raised about our product, claiming the validity of virtually all of our studies, saying that in fact there was more emphasis on the benefits rather than

Page 205

the harms. And this was by a credible spine surgeon, and it threw our company for a loop because it really challenged all of our data and suggested that the peer-reviewed publications actually were not valid.

The principal focus were really on the results of the peer-reviewed literature. There was limited or no concern about the data sent to the regulatory agency early on. And we still feel that the data sent to the regulatory agency was complete when we re-reviewed that data.

The focus was on how did the peer-reviewed publications emphasize or overemphasize certain benefits over harms in the peer review process. And it became a challenge for us because we don't participate in the peer-reviewed literature. As a matter of fact, we're admonished if we do. People don't want us to do ghostwriting or any kind of process interacting with that.

So we were challenged with trying to understand how to respond to this. It was a very serious accusation covered in the New York Times

Page 206

and seven or eight other publications. I was on the phone with Barry Meier the day after this broke out, and we had to really review a bunch of papers that came out, re-review our history, and take a stand.

So we decided that we were not going to fight a battle of our interpretation versus someone else's interpretation because it would be inappropriate. We also felt it was responsible for us to make sure that the public could trust us and view what this means. And we also wanted to understand whether or not these claims that were made were actually true, because if they were, we needed to take action on the product.

So we decided to take a process to try to establish what would be viewed from the public as an independent process to review the data. And what we did was, we worked with some colleagues that we had loose connections with at Yale, who had mainly an interest in data transparency. And we felt that that would be a good group to work with because they had already worked through a lot of

Page 207

policy issues about how to make data transparent, and they had a huge interest in trying to do this.

We agreed to take all of our data, patient-level data, to de-identify the data, have it audited -- that was for 14 studies -- and take all of the adverse event reports that we sent the FDA over the last 12 years, and all of the e-mails between the FDA and so on, and give that to Yale.

Then Yale, in their group, decided to -- we then stood back. We did not set the agenda. We said, "Here's all the data. Figure out what the issues are. Read these papers about what the concerns are. But what we'd like you to do is to provide for us a systematic review of our data so that we can understand what the truth is."

So they took that data. We stepped back. We funded it. It was about 2 and a half million dollars to fund. And we were very careful about making sure that we looked at where that money was being spent, and it was reasonable that it was being spent for things exactly as expected, the data processing.

Page 208

They contracted two separate, independent groups to do a systematic review. And they chose two academically established groups. One was the Oregon Health Sciences University, OHSU, and the other was York in England, both of which are distinguished systematic review groups.

So the connection between the systematic review groups who were going to evaluate our data was with Yale, not with our company Medtronic. Our relationship to Yale was to de-identify and give all the data to fund this activity, and then let Yale set the agenda about this. So Yale chose the systematic review sites, and they established the steering committee to review this.

The principals for this project -- and there was a chance that Harlan was going to be here to talk, but he had a conflict. And I'm not going to get into too much detail because it's really not appropriate to explain all of their processes, but I'll give you some high-level overview.

Harlan Krumholz is, I think, a distinguished health quality and health services researcher. He

Page 209

is the editor of Circulation Quality, and he has a group who has a major interest in understanding how to make data more transparent. So we worked with him.

He also assigned a steering committee to oversee this independent from him, just to make sure that there would be no concerns about his role in contracting with Medtronic, and that was headed by Zeke Emanuel, who had been on Obama's staff early on and helped shape the Affordable Care Act. And he led a group of distinguished individuals, about 15, one of which included Deb Zarin, for example, who runs the clinicaltrials.gov and others.

So we tried to develop what we thought would be a beyond-reproach group of individuals who have a history of not being influenced and also would be able to look at this case. So that's the basic structure.

The deliverables were that the systematic reviewers would produce two formal systematic reviews, and then the publication of that would be

Page 210

through a contract with the Annals of Internal Medicine, which is a top-tier journal in medicine. That would be, as a manuscript, summarizing systematic reviews. The sequence was that the systematic reviews would be produced. The systematic reviewers gave their initial reports to Yale and to us. We were able to make comments about that. They were not in any way obliged to follow any of our comments, and Yale made comments back to them. They essentially had the opportunity to revise as systematically as they wanted to or not. And we have not seen any results of that second round yet, and they are completely independent to do that. And they are in the process of finally getting the papers published.

This has taken us a little longer than we thought it was going to take because we thought it would be done within a year. It's been almost two years, but that's just the process of publication and reiteration. It was completely independent on our part. So we expect in June to see the manuscripts being published for these. There are

Page 211

summaries of these systematic reviews. That will be followed by the full systematic reviews, which are essentially these phone book-type detailed analyses of all of these studies.

Then on the third part, we decided in concert with Yale that we would make all that data publicly available. So the patient-level data that we gave to the systematic reviewers would then be made available to the public. And we're in the final process here, understanding how to make that dissemination, which is going to be a process we follow about how we take requests, and give the data out, and so on. And this is where we're finalizing that process. And we're anxious to understand what that means.

So that's the overall structure, per se. I wanted to show just a little bit about some of the processes involved in getting this data. It was very complicated.

In order to get the initial data that we had in our data warehouse for these studies that went back 10 or 12 years and make them available for

Page 212

systematic review, we had to go through a HIPAA de-identification process, and that was a very timely and costly process. Hopefully, if we get experience, we'll learn how to streamline this further. And these are not meant to be read, but we had extremely difficult --

MS. DILLEY: That's good

DR. KUNTZ: -- processes to follow. And overall, we -- there's an individual I have in here, and I'll speed through them because I don't want to waste time -- did hire a -- well, actually, Yale hired -- we paid for it, but Yale hired an expert. And there are these experts. This is a person on faculty at Columbia, who our experts and certified to do de-identification. And you have to de-identify about 13 different fields of the data in order for it to be processed.

So this is a first-ever in industry, in the drugs or devices, to ever do what we have done. So we were a little bit blinded in trying to understand how to go forward. So my guess is that we were very inefficient in some of our processes,

Page 213

and that's why it cost $2.5 million to do this one project. We don't think that to do this again is going to cost that much money as we start to get more efficiency. But what we were really focusing on was really understanding how to make sure that we could be trusted to say, "You know what? If there were mistakes made in our product, we need to know it as well as anybody else does, and we need to take appropriate action." But the first part is to really get the truth, and try and understand what that means.

Understanding that, with the discussion earlier today, that one would like to have total independence, one has to also understand whether there are resources available for those independent groups to do that. And since the profit-making companies like ours have dollars that we can spend on that, how do we basically take those dollars and directly put it into a system that can still be beyond reproach and be independent.

So we're anxious to see the final results of how this comes out. We're anxious to see whether

Page 214

our industry colleagues, our competitors, and other people in the drug and device industry think this is a good experience or bad experience. We want to make sure that it looks like a good experience because we're true believers that data transparency is very, very important to go forward.

We certainly would like to, as an industry, compete on the technologies that we make and not on whether we hold data back, and I think that's also going to level the playing field to make it a lot better. And I think everybody's in agreement that that's probably the right way to go.

I want to end just with a few comments about what concerns we have when we look at the transparency part. To make data transparent is a little scary. We have complex data that when held in silos and shielded from everybody are concentrated. People actually know how to do analysis and are actually very concentrated. And then this is shared by Food and Drug Administration people who also do these kind of analyses.

That's probably not the best configuration,

Page 215

but to liberate a lot of data to individuals who don't have methodological training, especially some of the complicated analyses, may cause individuals to find the wrong results. And there is still an appetite, on the media side and others, even journals, to publish sensational and outlier-type results. So we want to understand how to move to a space that becomes a little bit safer, so that we can get actually the truth as we start to disseminate this product.

We're committed to making the data publicly transparent, but we know there will be some turbulence in a way. Our announcement that we're going to make the data publicly available has already led to internet sites from plaintiff attorneys in Manhattan, who have already requested people to say, "When we get this data, please let us know if you've been harmed by our product because we're going to try to analyze the data." So we knew that, that was going to happen anyway. And so we're trying to figure out what the process is.

Page 216

So we want to know, for example, when we get a query, who is asking the question and why. Not that we would ever bar a plaintiff attorney's law office or group to be able to ask a question; they have just as much right as anybody to ask questions. We kind of want to understand what the question is to make sure that they're not trying to look at something that's just purely a money-driven approach on their part.

Should we limit these queries to one question at a time? This is what they do in the U.K. The U.K. has a transparent policy. They limit it to one question at a time, and they license the question. I'm not trying to ask the questions rhetorically to say we're going to come up with the answers, but these are things that you would have to go through if you're going to make a transparent process.

What about access? Do we just put this in an Excel spreadsheet and just send it out? That probably is inappropriate this time. Do we actually have another third party maybe help

Page 217

individuals who don't have the talent to be able to review or analyze stuff, do that independence if they know what the question is? These are questions we have to look at.

Then, finally, the methods are really critical because we spend a lot of time on product reviews, months with the FDA and panel to determine how to actually answer the questions we're asking, how to make sure we preserve type 1 error, how to make sure that we don't go overboard and analyze stuff up front here.

When we give and liberate a lot of data, there's a massive opportunity for type 1 error, for people to find a lot of probabilities. So how do you disseminate the information to make sure that the findings are treated as hypothesis-generating rather than as results of studies going forward, so that people don't get harmed, or that we don't exaggerate claims that we actually don't have.

The data-sharing part is really looking at how do we slowly disseminate this out further to people with or without those talents. And I'll

Page 218

just go to my last slide here.

I think what one of the most important questions that we want to disclose in this space is what our role is on the industry side. And I'm from academics, so I've got sensibility about what the academic side is as well. But in industry, it was our role?

Our role principally is to work with a regulatory agency, and make sure that we follow regulatory guidance, and make sure that we get a product that has regulatory results that meets standards so that patients can be informed.

We currently work with a separate sphere, which is the peer-reviewed literature sphere, where principal investigators publish and take our data and publish it in that realm. And that is regulated by two reviewers, and a publication, and a journal. And in many cases, it's very difficult to understand whether or not we have a role in policing the peer-review process.

It sounds a little ironic. The industry-policing, peer-reviewed, independent

Page 219

review, that's probably not appropriate. However, there are plenty of examples where principal investigators are just as motivated to make things look as good or better than the industry may do, or that they may actually be well intended, but may not analyze the data correctly because they don't have the skillsets and that happens a lot.

So we need to understand -- and we do this, by the way. We have several businesses, and I can tell you many examples, where our side actually cautions the principal investigators to not make these claims because they're not real, and we talk to this all the time. Nobody ever covers that in the New York Times, by the way, but that happens a lot in our company. But there are no rules about this up front.

So anyway, that's the model that we did. It's a 15-minute conception of a very complicated process that we went through. I outlined, I think, a little bit of the structure about what we try to do to answer these questions to go forward with the main intent to have high integrity on our part.

Page 220

We feel, and our CEO feels, that we can weather the storm of a product that may have had some problems that we may have had to take off the market. We can deal with that. What we can't deal with is having anybody view us as not having high integrity because that's where companies go down.

So we need to maintain that philosophy that we can be trusted at every level, even at the risk of saying that we made a mistake or that there is data that came up and we need to pull something off the market. That's a structure that we want to develop. But there are derivatives of that, and that includes issues about how do you go to this next level of responsible data sharing and handle the processes. And I'll stop there.

(Applause.)

MS. DILLEY: Thank you very much. So I'm going to start with an e-mail question, if I could, because I'm very excited that we got one that was e-mailed.

(Laughter.)

MS. DILLEY: So the question for you,

Page 221

Richard, is what will you do if the results are not favorable? I think you've already referenced that. And then a second question, do you plan to use a similar process for other products?

DR. KUNTZ: Good questions. We'll act appropriately whatever the findings show. And the actions will be everything from taking the product off the market to reinforcing the claims, if they're shown to be important, to modifying the claims, to inform patients that there are high risks that we had talked about before, that they need to be informed on. So it's a continuum.

There is some room for products to be able to inform people about benefits, and risks, and the changes in that ratio. And then there's a point where the ratio becomes unfavorable, and you need to take a product off the market. As the product becomes less beneficial and more risky, then we have to focus on those individuals who most benefit from the case.

So in the case of BMP, we know that there are some patients that have osteoporosis that just

Page 222

don't have good responses from normal therapy, and this is what they need. And they may actually tolerate a higher risk-benefit ratio if that comes up. But the individuals who would have perfectly good responses from alternatives, that may cross their threshold and they decide not to use this product because the risk profile has changed overall.

So I think what we would want to do is just make sure that we look at this, and we intend to use third parties to also gauge this risk as well, so that we can make the appropriate part. But the relationship we've had with the FDA has been very good, and I think, in general, they'll weigh in very heavily on how they look at this data and whether or not they think action should be taken as well, and we'll follow that appropriately.

MS. DILLEY: So they obviously get that information at the same time. Right?

DR. KUNTZ: Yes. And the second part of the question is, will we do this for the data? Yes. We will. We're actually looking at the next

Page 223

product. What we want to do is make sure that -- I'm very concerned about jumping out too far ahead at this point because if we get burned, it'll really push industry back many years.

This is something I think that the Yale group is very cognizant of. Of course, they would like to get instant transparency immediately, but they also know the practicality that if in fact we put three or four products on the market right now and then we had ended up with hundreds of millions of dollars of lawsuits, we know that our industry colleagues will pull back the circle wagons and say, "This is not what we're going to do."

So we want to have this as a good experience going forward, but we do intend to bring, within the next year, another two products to the public, and then try to get broader as we start to understand how this stuff works.

MS. DILLEY: Great.

Joanna, you had a question?.

DR. COHEN: Joanna Cohen from Johns Hopkins. Just a question of clarification. It's your slide

Page 224

number 8, which is communication, logistics, and boundaries. And you had some bullets of the team can communicate about certain things and the team cannot communicate. So my first question, is that your team?

(Brief pause.)

DR. COHEN: So the team is who? And my second question is what's the difference between study conduct and evaluation methods?

DR. KUNTZ: I'm not quite sure exactly what they meant on here because its the internal part. I can tell you that we designed this to make sure that -- we wanted to make sure that our team didn't influence in any way the processes that we did.

So when we talk about evaluation methodologies, we wanted to make sure that they were free to do evaluations differently. We had some insider baseball approaches that we used in evaluation of products. And so when we discussed how we would do the data, the first part was, we can give you studies we've done and so on, but we want to be very careful about understanding the

Page 225

algorithms, assess codes that we use to evaluate the methods to make them freely available.

There is nothing nefarious here. We in many ways want to make sure that everybody got all the data we had, but we were restricting some of the things. We might be viewed as being influential if we were to tell them, this is how we did the principal analysis of the study. This is why we think we showed benefit. Here's our methodology used. In situations like that, we said we weren't going to do those evaluations. And that may be what that states here.

MS. DILLEY: So that's trying to set up the firewall between what information you're doing and what you think might influence the --

DR. KUNTZ: Yes. These processes were actually a team effort between Yale and us to say, okay; how are we going to keep this data together, with an idea towards making sure that we show this publicly; it would be clearer. But I know we failed on that. So I'll try and make that more clarifying.

Page 226

MS. DILLEY: Redesign on the boxes.

Do you have a question over here?

MR. DILLARD: Richard, Jim Dillard. Altria Client Services. A clarifying question, and then maybe a little bit bigger question, which is, if I have this right, there was about 14 studies. They were all pre-market studies that were done.

DR. KUNTZ: No. About half.

MR. DILLARD: About half. And then that other half is what you've been doing in the post-market period.

DR. KUNTZ: That's correct.

MR. DILLARD: So you took all that data and did what this appears to be as a post-market re-analysis of sort of the ongoing data up to that point. Is that correct?

DR. KUNTZ: Correct.

MR. DILLARD: I've got that clear.

Would you ever venture down this particular pathway and do something similar -- I probably can't answer it at this point, but you've thought about it, I'm sure -- as a secondary data

Page 227

re-analysis before you ever got approval for a product?

DR. KUNTZ: Yes. So this is a really interesting question. The way that devices -- and I think drugs -- is that we do pre-market studies to meet some endpoint, usually in time, to get approved. And usually, those endpoints are on the one- to two-year range. However, there's a huge interest in long-term durability, risks of things like cancer and other stuff like that, that we can't necessarily wait for. Otherwise, you're going to get technology that's very, very stale.

So we hope that that handoff will happen in the post-market. And it's one of the reasons we do post-market studies. We continue to follow those patients and new cohorts for a longer period of time and update that. So that's one of the reasons that we do post-market studies. And then, we're also introducing the concept of doing more appropriate surveillance to look at those as well.

So we don't necessarily do a systematic review in the pre-market application for the PMA

Page 228

together. We just get the data in, and then they're actually listed as separate trials. But I think we are starting to see some value of doing large, systematic reviews of all of our data to be able to track rare events and other things as well. And we're doing that for coronary studies, for example, and others, especially when you start to collect data sets where there isn't enough power to look at these rare events in individual groups themselves.

So, yes. We are going to be doing more systematic reviews of our products overall, not only because we're curious, but because the demands of the people who make the buying decisions want to know that data as well, including the patients and caregivers.

MS. DILLEY: We have time for one more question. Does anybody have a question?

(No response.)

MS. DILLEY: Great. Well, we'll come back to you after Eric gets his presentation, and Mark as well.

So next up, we have Eric Peterson, who is the Fred Cobb professor of cardiology in the Department of Medicine, director of the Duke Clinical Research Institute, and the director of performance improvement for the Duke Heart Center.

You even have time to give other presentations elsewhere. Thanks for being here.

Presentation – Eric Peterson

DR. PETERSON: Thank you very much. Just another comment on that last question. In part, there is another entity that has access to all those studies and can do those meta-analyses. That's called the FDA, when it's going into the pre-market setting. So theoretically, it is a third party that's overseeing, at this case, the regulatory party.

Before I begin, I'll do some disclosures. In part, I am part of an academic university. I do here -- although we don't know anything about any tobacco monies that ever come in to our institute, at least as a part of this -- however, we do receive a fair degree of our funding -- up to a

little over half to two-thirds of our money does come from the device or drug industry with regards to both on the pre- and post-market effort to try to establish the evidence and is ultimately to drive those into practice.

We are by our title, and at least our own claim, the world's largest academic research organization in terms of the types and quantities of work we do. We're over 1300 people right now, working on our single institution, devoted to this single mission. And we believe very strongly in this, this idea that we are, in part, charged to help develop and share knowledge around the world to improve patient care through innovative clinical research.

Conceptually, this is the idea that we, in part, want to try to get the best evidence known, and then to share that in a manner that helps patients, and then to try to do it around the world, and ultimately to drive it into clinical practice.

In concept form, it's the mergers of two

worlds that have lived in very different and sometimes highly competitive worlds, maybe three. In part, there is academic centers. And you heard this morning about experts in the field. We're trying to marry that with the abilities of a contract research organization, or CRO, conceptually that we can do the parts of research to produce high-quality, very efficiently run research, but now married to this mission as opposed to married to a bottom line that's going to produce a profit.

So rather than being a standalone industry that's going to produce me as the executive, a fair degree of money, unfortunately for myself at least, this is more about the mission of trying to produce better evidence.

The DCRI grew. It's sort of an interesting history. I won't give you the full story of it. But it was started by our first chairman of medicine, who took a government grant that was supposed to be about how we might use computers to better understand systematically how patient care

should be delivered. He took that data, collected information on however patient with cardiac at Duke was treated with an idea that if we learned what was being done, maybe we could learn better how to do the next one.

That created a generation of statisticians and clinicians working together, and ultimately created the need for maybe observational data alone wasn't enough to answer these questions, so we would do randomized clinical trials, which then led to the world's largest, at that time, clinical trial, the GUSTO study, which then launched a whole series of other studies after that, and that became us. It has now expanded into a lot of different realms, and I'll go through just a few of those.

If you take it at its whole now, we do sort of three forms of research. There is clinical trials, everything from the earliest phase 1 or first-in-man studies, all the way through phase 4 type of research, post-market studies.

A lot of that research is done with the government. We conduct large studies that

Page 233

are -- large network trials with NIH in particular, but with other agencies as well. And then with industry, as we mentioned before, in part, these are often looking at a specific product, does it work or not, and helping to develop with industry in those cases whether or not those drugs or devices are safe and effective when used in humans.

We also do outcomes research, which is the idea that we might use evidence that's available in other forms, either from claims or clinical registries to, in part, learn about the safety and effectiveness of drugs or devices when used in routine clinical practice, and where there are gaps in care, and ultimately to drive that forward.

Finally, we're getting more and more into the educational sphere, and I'll talk about this later. But, conceptually, this is another one for which huge conflict of interest issues have certainly limited the scope and quality of research or quality of education that exists out there, and it's our goal to sort of expand that role as well.

We believe that, like a CRO in part, we can

Page 234

provide all the expertise on how to execute a study, the operational component pieces, but also have, from a design perspective, the ideas that a clinician and a regulator might want in terms of how to develop the best evidence; and then ultimately the analysis capability to carry out that research, get to the right question; and then hopefully the role of education to try to teach our peers and the public what we ought to be doing with this evidence.

We do this on a global basis. We have partnerships now. There's a BCRI in Brazil. We have many partnerships in China. We have a few partnerships in India and partnerships in Singapore. In part, research has gone global and, in part, we now want to partner with either academic research organizations around the world or, alternatively, our own partnerships to try to further these research activities.

Just a few words I put in this slide -- this isn't in your packet, I'm sorry -- to try to get an idea of how these studies are created. There was a

Page 235

lot of discussion about that before. In part, there is a combination of forces that come together to create a study design. Many of it are set forth by the FDA under their regulations. Scientific experts come together, coordinating group come together with co-chairs, often international representatives from science in the field, to create the study design.

Then that's taken to the FDA and, again, there is a blessing and a hand-off between those two groups to say, this is an acceptable or unacceptable design; your control was accepted, et cetera. All those kind of questions are vetted backwards and forward until an actual final study design is created.

Sponsors do work with that, in part, absolutely. But, again, it is a collaborative process to try to get the best science with regulators on the top of it to make sure that the process is ultimately fair. Data safety monitoring boards are out there to monitor the activities and safety for the patients that are involved, and

Page 236

clinical events' committees adjudicate the degree to which the accuracy of many of the elements, in particular the endpoints, that come out of the study itself.

As we mentioned, that's sort of on the trial side. On the observational research side, there's a whole plethora of data that I won't be providing today, that talks about how we might look at real-world information to try to create a more clinical knowledge.

We're getting more and more sophisticated at using data from either electronic healthcare records or, alternatively, clinical claims models of data, linking data in various fashions, linking it now to genomic and other information, biomarkers, et cetera, even now looking at the drugs or devices, to create better evidence from comparative effectiveness and comparative safety studies.

Then finally, we're moving to a world where there's not going to be this division between observational data from registries and clinical

Page 237

trials, but there will be hybrids created. And we're working very fast at trying to create practical clinical trials. In our view, this concept of registries and trials working together much more fluidly will ultimately produce cheaper but more accurate studies, maintaining the role of randomization, but in fact trying to make these things a part of routine clinical practice when there is a lack of evidence about what the best thing is to do.

This probably will be less appropriate for devices or drugs that are new to market, but more appropriate for things that we might be using or standards we might be using out there, but we don't know which one is the most appropriate.

We are carrying out these right now -- this isn't all just sort of myth and future hype -- in part, with the Cardiology Society of America, who holds their national registry. We are the analytic center. We're creating a randomized clinical trial of two techniques on how to access your coronary arteries in women to do angioplasty procedures

Page 238

through the groin or through a wrist procedure. This will be a randomization at the level, but the data is all collected within the registry itself, so making a much more efficient study.

Then probably the most unique hybrid that is coming out now through the collaborations of the professional societies is a new device for percutaneous opening of heart valves, percutaneous placed aortic valve.

This has industry partners, the FDA, CMS, and the professional societies, as well as an academic party, all working together to impart every patient that's going into these, who have these new devices put in. They'll be put into a national registry. That will be used for both research purposes, ultimately post-market surveillance; and then even extensions of indications in settings where they think they don't need a randomized comparison.

Ideally, this will have multiple industry partners playing, using all the same registry, so it can happen when done in a right setting. And

Page 239

then there is some work even beyond that, efforts to use electronic healthcare records across major healthcare systems, called the Collaboratory Effort, sponsored by the NIH. We are the coordinating center for that activity, to try to, again, stimulate more clinical research in very practical clinical studies'; again, emphasizing the role of randomization, but trying to do it in a much more simplified fashion.

We produce a lot of papers out of this activity in any one year out of the DCRI. It's nearing almost 900 publications that come out of that. Over 20 percent or more will be in what we call top-tier or high impact journals, so the peer review process is a large part of what we have to go through.

But I will emphasize just one point upon that factor that came up earlier about how to avoid spurious findings. Rick mentioned this earlier. But we believed very fully that part of this can be gotten around by actually having, just like within a clinical trial, investigators put up front what

Page 240

the actual question they're going to ask is, what the endpoints are, how they're going to analyze the data to avoid fishing expeditions.

I am also one of the editors for JAMA, and I am trying to press this very hard into action, so that we will be able to have a pre-specified analysis plan, to be looked at, at the same time we have a journal article, particularly those when used in observational research.

Then finally, we are doing a fair degree of work of trying to push this data out into the real world -- I won't go through that today -- as well as efforts to try to improve the continuing medical education process, which has also challenged some of the discussion earlier about how will these messages be conveyed to the public, apropos here.

We're trying to develop the academic centers to be a home where high-quality education could be developed, but hopefully in more innovative strategies than have been used in the past. So that was a quick run-through.

(Applause.)

Page 241

MS. DILLEY: Why don't we just take some quick questions for Eric? And then Mark is going to come up and talk a little bit, then we'll go to our panel. But for Eric, questions for clarification?

MR. MYERS: Who designs the studies? Do you do it or does the company, or is it a partnership?

DR. PETERSON: Yes. I will repeat the question. Who designs the studies? And in that regard, it's a partnership between the academic center and the sponsor, ultimately the FDA having a large oversight in terms of okaying or not okaying the design that's been put forth if it's an investigational drug or device.

MS. DILLEY: Other questions for Eric in the overview?

DR. PETERSON: One more question, I guess. There was discussion earlier today about the degree of independence and how that would be maintained. And I think most academic centers, we had to sign a pretty strict contract with our legal services that would say that any data that we've gone down the

Page 242

road of saying we're going to investigate these things, we have a right to the data, to publish it, to use it for any publication that we want to go forward with. Industry has a right to see what we will be putting out and comment on it, as mentioned by Rick, but not to rewrite what we are or to withhold that data from publications.

Just to tell you, in my experience, while there are bad experiences out there, I've had more difficulty publishing things from my own professional society than I do from industry. But you could argue whether one's in industry and one's not.

MS. DILLEY: Another question?

MS. COHEN: This question is for Duke. What role does a funder play in design, conduct, and decisions about publication of research? Are any of the concerns raised this morning about independence of researchers addressed?

DR. KUNTZ: Yes. I think there might have been a time lag, and I anticipated the question, so I think I handled most of those issues.

Page 243

MS. DILLEY: So Mark, I know you were going to start thinking around translating some of this information that both Richard and Eric have provided to some of the questions raised this morning on third-party governance for tobacco-related research. So we'll turn it to you and then we'll have you set up with the other two.

Discussion (continued) – Mark Parascandola

DR. PARASCANDOLA: So great. I think it is helpful to hear examples of how, at least in other research arenas, people have implemented research governance structures. And I think this is helpful to get us started.

These are certainly rigorous models, I think, for research governance. But I just want to move us into a discussion just to give a few brief bullet points about special issues that may be addressed in trying to do a similar thing in tobacco product research.

So first of all, I think the issue of ethics in human subjects protection, that's kind of built into clinical research endeavor in these days

Page 244

because of regulations from both FDA and also that apply to NIH-funded research. But before the Center for Tobacco Products, tobacco product research that was not funded by NIH was in kind of a no-man's land because it didn't fit under -- if it wasn't funded by NIH, they didn't have to follow the common rule as a PHS-funded research does. And if it wasn't submitted to the FDA as part of a new drug application, they didn't have to fulfill those requirements.

So I think, first of all, it would be helpful to have some more attention to application of the common rule to human subjects research that's conducted in the context of an application to CTP. And I think also it's important to consider the human subjects protection in this research context. So at NCI, we have seen a number of unique ethical challenges or questions posed by IRBs to our grantees. IRBs have different views about how to assess the risk-benefit ratio in evaluating potential modified-risk tobacco products.

Page 245

Some IRBs have raised concerns about giving an experimental tobacco product to research subjects. The product itself, of course, poses risks and then there may be other risks that are unknown. And so we really kind of lack guidelines here for how to evaluate those kind of risk-benefit questions in the context of potential modified-risk tobacco products. So I think that's an area we need to look more attention to.

The second point I wanted to make is I think we need to have more attention to what the scope of industry-funded research is that we're talking about under these governance models. I think this is the theme that actually came up already this morning, so I'm not going to say a lot about it.

Not all research projects may require the same governance model. We might distinguish, for example, as has been said this morning, between studies that are conducted in the context of providing data for a specific modified-risk tobacco product application versus studies that are conducted to develop novel methods for assessing

Page 246

tobacco product risks or more exploratory research that investigates the characteristics of different tobacco products.

So the public health standard that's written into the legislation requires that research is conducted to inform and develop methods to apply that standard. And we don't currently have a set of methods to evaluate modified-risk tobacco product application. So I think this is really a key priority, to develop methods and thinking in that area.

Third, I think the question of who sets the research agenda has also come up. There are general research needs, as I've said, around developing methods, developing and validating methods for evaluating novel tobacco products. But then, there are also going to be research needs in the context of a particular modified-risk tobacco product application.

So in thinking about third-party governance, I have to think about who is asking the research questions. And the way this is conducted in the

Page 247

context of the pharmaceutical industry may not necessarily be the same in the case of tobacco.

Fourth, transparency and access, of course, is key. And I think Dr. Kuntz mentioned that, sometimes, opening up a data set can be scary. And I think this is a double-edged sword, that of course we want to promote transparency, but also data can be re-analyzed and manipulated in ways that are counter to the investigator's intentions and counter to public health. So that's, I think, additionally a concern we want to address.

And finally, there is certainly a burden imposed on industry to meet these standards. And I think that's appropriate because the stakes for public health are very high in assessing or evaluating a novel potential modified-risk tobacco product.

So there's a burden on industry also to show, through their behavior, that they are conducting and supporting rigorous and valid science. Again, Dr. Kuntz mentioned that Medtronic is planning to make additional data available from

Page 248

their studies. I think tobacco companies could certainly be encouraged to do the same, to make as much of their own research data available publicly as possible, independent of what other funding and governance structures there may be.

So I think beginning to put that kind of transparency into practice would be at least a good first step. And at the same time, we need to develop independent research capacity to study modified-risk tobacco products and conduct research in this area, and, in general, to increase our capacity to understand the nature and characteristics of different tobacco products and their effects.

Really, I know from my place at NIH that there is a relatively small cohort of researchers who are working in this area, studying the tobacco product itself. And we don't have the sort of worldwide network that Duke and others have built up around tobacco product research. And I think it's going to take time and effort to build up that kind of independent expertise. So that's another

Page 249

issue for consideration.
So thanks. I'll stop there.
MS. DILLEY: Great. Thanks.
(Applause.)
Q&A Session – Abby Dilley
MS. DILLEY: So we're going to open it up for questions for all the panel. David, why don't you start us off?
MR. DOBBINS: Hi. This is Dave Dobbins from Legacy. You had mentioned -- and this is for both of you. But you had mentioned that the FDA, obviously in clinical trials, ultimately approves of and understands your design of your study. But I take it -- or maybe I'm wrong -- that the FDA has never at some point made some sort of declaration that the Duke Center is a great center and we can rely on the research coming out of it a priori. It's studies based on the particular study at hand.
DR. PETERSON: Right. It's only the NCAA tournament that lets us get in at that same criteria. No. Sorry.
MR. DOBBINS: I actually believe that.

Page 250

DR. PETERSON: Sorry. I couldn't resist. I could not resist.
No. You're absolutely right. I mean, it's not a matter of who brings the study to them. I do believe there's some credibility that comes perhaps with an independent grouping involved in it rather than an alternative source. But, truthfully, at the end of the day, the design has to meet the FDA's rules.
MR. DOBBINS: And, I mean, I take it -- I mean, I'm not trying to cross-examine you, but, I mean, I take it that you would agree that that credibility has come with performing, again and again, reliable studies that the FDA has seen. Right. And that's sort of my point.
MS. DILLEY: We have another one from e-mail, so this is to you, Richard. Your last slide has a bullet that says, "Free to discuss any results if not sponsored by industry." Can you explain what you mean by this?
DR. KUNTZ: Could you say that again?
MS. DILLEY: Yes. It said, "Free to discuss

Page 251

any results if not sponsored by industry," I guess, on the last slide. This is another one of your boxes, I think, that maybe you had --
DR. KUNTZ: This part, I did write.
MS. DILLEY: Oh, good.
DR. KUNTZ: I just want to think what the context was on that, "Free to discuss any results if not sponsored by industry." Well, I think I was just making a general statement that when you make it publicly available, you allow perspectives outside of industry to evaluate the product.
So, I mean, the general statement is, as much as I believe that we act responsibly and try to view the data as clean as possible as we can with the patient's best interests in mind, we can't always make that statement because we have a psychological overlay of conflict. This has been straightforward, and this has been studied by psychologists and sociologists and those forever. And the notion is that what we need to do is find that forum by which other perspectives can analyze the data.

Page 252

So I think that's what that statement means, is that essentially we will always have a tendency, whether we like it or not, to try to shine on the benefits more than the risks. Now, all our patients -- we take care of other patients as well. We'd like to hope that we would never do that, but the problem is that nobody is going to trust us in that situation. What they will trust us is to have a process to be able to get that data for other perspectives to look at.
So I think what it states -- what it means is that we want to have people be able to discuss and look at data from other perspectives.
MS. DILLEY: I don't know if we talked about this, this morning, but there's a difference between conducting the studies and then looking at the data separately. The studies were actually conducted by Medtronic. Right?
DR. KUNTZ: That's correct. Yes. Well, they're conducted by -- I mean, they're run by clinical science.
MS. DILLEY: Right.

Page 253

DR. KUNTZ: I mean, that's what they're run by. And so the ultimate responsibility of the data comes from the clinical sites, hospitals and clinics that enter the data into the form, which are monitored independently.

MS. DILLEY: Questions? If you could, introduce yourself.

MR. RUTQVIST: Lars Rutqvist. I have a question to Dr. Kuntz. Could you please elaborate a bit on the nature of the contacts you had with the FDA before you embarked on this impressive effort that you described? Did you get feedback from the FDA?

DR. KUNTZ: We immediately informed the FDA. Now, let me give you a little detail about the process here. I will say it wasn't an optimal configuration about how this happened. An individual with well intentions decided to dedicate an entire journal that he was editor of to this issue about our product with 10 or 15 articles. He submitted those articles initially to the New York Times. So we heard about it through the New York

Page 254

Times.

This was a Friday afternoon. I was ready to go see my kids play baseball, and I get this call from the New York Times, saying, "Monday or Tuesday, we're going to publish this paper. Here are 15 embargoed papers you should read about. I'm going to call you on Monday and see what your response is."

So that was not what I thought was a very optimum way to potentially challenge or go through that. So what I did immediately was inform the FDA to say, look, this is what I just learned. Here are the articles. Take a look at this because I want to make sure that we're clear with you about what these issues are. And while we had informal interactions with the FDA, what we wanted to let them know was our process was going to be to clear this up front here.

So I'm sure that they did some internal review of their data. And I don't think anybody's ever challenged the data that we submitted 10 years ago to the Food and Drug Administration. As a

Page 255

matter of fact, that's never been challenged. This data is there. The question is how did it get disseminated through peer-reviewed publications, is my conclusion about how this issue dried.

So the FDA was fully informed on this. They had been asked questions at public sessions about this, and they felt that they were anxious to see the results of this independent review. I can't speak to whether or not they did their own internal review on this as well. But I think they probably stand behind their initial review and panel results 10 years ago.

MR. RUTQVIST: But did they provide feedback on the scope of what you did, or did they come up with suggestions as to extra components of the review?

DR. KUNTZ: They were supportive. They were clearly supportive of our process. And while we didn't engage them in the process -- because I think that would be inappropriate both on our part and their part, because they weren't asked to do this -- we let them know what we were going to do

Page 256

with Yale, what our processes were. And they had, obviously, the full opportunity to come back to us and say that they did or didn't agree with that. So I think there's a tacit agreement that this was probably a good process.

MS. DILLEY: So you weren't looking for approval. You were looking more for red flags.

DR. KUNTZ: This is all novel. This is new. Nobody's ever done it before.

MS. DILLEY: Right, right.

DR. KUNTZ: So our issue was to make sure that we were just informing as many people as we could about what we were doing, and it seemed to be consistent with what their goals were.

MR. RUTQVIST: Thank you.

MS. DILLEY: Other questions?

MS. LEE: I'm Monica Lee from JTI. Perhaps it's more general to all the panel members, if that's okay. I was a bit surprised because we talked about types of research, but if you focus on MRTP, there is already draft guidance out there. The IOM report came out in 2011 and, as everybody

Page 257

knows, about several months later, FDA issued draft guidance on MRTP and what kind of scientific evidences. And I believe a lot of recommendations from IOM in terms of scientific evidence -- for example, importance of clinical studies -- reflected in the draft guidance. But the terminology of third-party governance I believe is missing. However, some components that I think we all talked about today, some essence seems to be there.

For example, the sensitive subpopulation testing FDA recommends discussing before the conduct. And at the end of study, all the data in the report would go through mandatory review by TPSAC, as well as released to the public.

So that is quite a lot of governance checkpoints in the draft guidance, and I was wondering how the panel member feels about those checkpoints are still not adequate. We still need another third party. Or not?

MS. DILLEY: You're asking to their particular products and the relevance for their

Page 258

governance, or are you talking about MRTP?

MS. LEE: I'm talking about MRTP. If the essence of a third party is to make sure transparency, reproducibility, all that, it has to be reserved, is the checkpoint currently the draft guidance; it is something relevant to meeting of needs of the third party? Or are we talking certain studies or certain checkpoints, that currently presented as a draft guidance, we have to use as a third party? Is that their recommendation?

So it's just a general question to the panel members, I guess.

MS. DILLEY: Richard and Eric, I don't know if you want to respond to MRTPs in particular, because that's not your area of expertise. But, Mark, if you want to do that, and you're also obviously welcome to comment on it.

DR. PARASCANDOLA: Yes. I can respond first. So, yes. There is FDA guidance on what kinds of evidence maybe would be looked at in evaluating an MRTP application. But a couple of

Page 259

points. First of all, that doesn't say what the methods are that should be used to conduct that research, exactly what tests need to be done to develop data to submit as part of an MRTP application. The reason is because I think, scientifically, we're not quite there yet. We don't have, say, a battery of tests that we can apply to say whether a product meets the standards for an MRTP or not. I think that's something that requires scientific study and investigation to develop. I mean, I can't speak for FDA, but I expect that that may be their intent.

Secondly, as to why we need a third-party governance, the third-party governance is not so much directed at evaluating the methods. I think it's really ultimately for FDA to decide what evidence is adequate to meet the requirements. But the third party is more to oversee the conduct of research, and I think that's the context we've been talking about so far, is that it would be -- if such a mechanism were to be established, it would be ensured that the data is collected in a way that

Page 260

it can be credible and reliable.

MS. LEE: Just a quick comment. If you're talking scientific integrity, in many points, I think for example GRP, GMP, as well as IRB, has been already addressed in the draft guidance. So that's what I'm trying to understand; what additional benefit or we are lacking in the draft guidance. Because the draft guidance is not just the type of study. It's how the study has to be conducted, how the public health standard has been met. And I believe you must have read it. You must have read it.

So I'm trying to understand, reconcile, the draft guidance, what FDA is recommending versus what additional guidance is necessary to meet the goal of the public health standard. That's it for me.

DR. PARASCANDOLA: Well, again, I can't speak for FDA, but speaking from the scientific community, I think there are still gaps. And as I said before, I don't think we have a series of methods that are well-accepted across the

Page 261

scientific community to evaluate whether a potential modified-risk tobacco product really is a modified-risk tobacco product or not.

So far, the requirements that have been suggested are very general. I don't know that we have worked out all the methods for how we get there yet.

MS. DILLEY: So I have an e-mail question.

"In your section on roles and responsibilities, Richard, of the different sectors, listed under academic reference, it said that, 'Academics are free to discuss any results if not sponsored by industry.'

"By contrast, Eric said that at DCRI, sponsors provide cash, but once DCRI gathers that data, they have freedom to do what they want with it.

"With MRTP, does Mark think --"

(Laughter.)

MS. DILLEY: If there were two other panel members, we'd have questions for them. But "Does Mark think that the DCRI approach makes more sense

Page 262

or would the Medtronic view be acceptable?"

So just trying to think of those different -- and I don't know acceptable based on what, but it's a question to you, Mark, ultimately, in terms of thinking about the different elements of those models.

DR. PARASCANDOLA: Well, I don't want to pick favorites among my fellow panel members.

Well, yes. I don't think I can -- I mean, I think the purpose, as I understand it, to hear about these others models, was to provide us some context for different mechanisms for providing research governance. But I think, as we've heard this morning, there are still a lot of unique issues around tobacco products research that are very different. And some of those concerns -- it wasn't the intent for Duke Research Center or for Medtronic to address those issues. They had their own set of concerns they were addressing.

So I think this is informative, but I wouldn't say that either model is going to be the one that we need for tobacco products research.

Page 263

MS. DILLEY: Based on two 15-minute presentations, I don't know why not.

DR. PARASCANDOLA: Yes.

MS. DILLEY: No. I'm just kidding.

DR. PETERSON: May I comment just a little bit more?

MS. DILLEY: Yes.

DR. PETERSON: I mean, I think the concern is that, is there ways in which potentially studies could be done and the information not be available in a way that could potentially have meaningful ramifications on health that wouldn't be released in some other fashion. And I think there's lots of different ways to protect it. And you've heard multiple parts of that -- Camel now -- through these presentations.

One of them even begins with the clinicaltrials.gov kind of thing, registering all studies that are going forth. At least you have a record of that. As you go further, you get to a point of, yes, if the investigators who did the study have access to the data and can publish it in

Page 264

a way that's fair and impartial, that's a very good check.

The third level is the FDA, obviously, when it goes to market has access to all the totality of the data and provides a regulatory review of the information, as was again described on how products come.

Then the final thing is looking at both the peer-review process. And then ultimately perhaps the most extreme, as what Medtronic is undergoing now, which is putting out the totality of the data for a systematic review. And I think that those are all remarkable but complimentary checks to try to get better access.

MS. DILLEY: You don't necessarily have to pick one best one. There are different ways of putting checks in the system. So I think that's a great way to lay it out.

Yes?

DR. KUNTZ: We might want to just show that there are three basic models to collect data. And maybe the analogy could go over to tobacco. But

Page 265

one is that a company like ours will both write the initial protocol approved by the Food and Drug Administration, conduct the study, do the analysis, and submit that to the FDA for approval. And that's probably our main approach.

The second is that we would hire Duke to run the study and collect the data. And we would, together, write the protocol and work with the FDA. And then they would do the analysis and submit it to them.

A third would be that -- which was never done, I don't think, in the industry, is that someone like Duke would actually do the study independently of the company and evaluate our product somehow. That model has never been developed, I know, especially in the pre-market.

I think what you'll find is that all three of those models have very traceable and monitorable processes, because the FDA is so rigorous with respect to how they set up stuff. The difference is going to be in the analysis and the emphasis. And that's where I think we have to just make sure

Page 266

that everybody's aware that that's where the promise -- we hope that we would be able, in all three of those models, be able to demonstrate that we could trace, through monitoring the data validity, the source documentation. And all the monitoring processes with all three models have to be meeting certain high standards, and they are high standards.

But when we get down to understanding what to emphasize, and what not to emphasize, and what to look at with respect to how we report adverse events, and so on, is I think where the public comes in, because then everybody can view this themselves and analyze this.

So I don't know if that helps develop the structure a little bit more, but if we get into a situation where we have more rigor with respect to how the data is collected, then you have a great vehicle, so it doesn't really matter who's doing it. It's really about getting the data available for analytical purposes.

MS. DILLEY: Thank you. Let me go back

Page 267

here. We had another one back here, and then up here to David.

We've got time, David.

MR. ROULET: Steve Roulet from Philip Morris, International and my question is to Mark. You were talking about global expertise that the FDA might benefit from. Could you be a little bit more explicit, maybe, knowing that the FDA is the only regulator so far that has created guidance for MRTP? Which area could they benefit from international knowledge?

DR. PARASCANDOLA: Well, I think there are many areas where they could benefit from. Although there's a large network of people who do research in tobacco control, treatment of tobacco dependence and this sort of area, there are relatively few really who study the characteristics of tobacco products, say tobacco product chemistry, the toxicology of tobacco exposure, as well as the kinds of clinical evaluations that would need to be done, and all the population studies that would need to be done to meet the public health

Page 268

standards.

So I think there's a whole array of -- and I can enumerate them all. But there's certainly an array of disciplines that would need to be involved. And right now, there is -- yes, I think the capacity is still limited for research in that area. Certainly, we hope to see that change, and I know NCI is funding more research in this area, and I think it's important to develop that independent capacity.

MS. DILLEY: I thought we had a hand back here.

MR. WALKER: Jeff Walker, Altria Client Services.

Dr. Kuntz, I have a question for you. I know Medtronic to be a very thoughtful organization. When you had this opportunity presented to you on Friday afternoon, you had a number of different courses that you could have taken. You mentioned notifying the FDA.

The question was, by sending this out into sort of a different construct that hasn't been

Page 269

tried before, how will you think about what to do if the results come back mixed. Adverse? And what's the role of the FDA? And because they regulate your product, does this take the decision away from the agency and gives it now to Yale? Gives it to Medtronic? How does the FDA play back into the role in going forward?

DR. KUNTZ: It's a good question, but I don't know if it's much different than a normal post-market study would have. So say, for example, the more common approach is that we do a post-market study looking at the long-term duration or benefits of an implantable device, and we find that, in fact, there are some negative aspects as opposed to the positive that we had hoped for. But then we work with the FDA to determine what the best course of action is.

It's our responsibility to make that initial communication with the FDA, and to be as quick as possible, and then to get an initial gauge, is there something we need to do tonight? Is there something we can do in a week or so? And what are

Page 270

the issues? And then appropriately act.

I think we'll follow that same model because, ultimately -- and, by the way, I just want to make sure that, in this process, Yale and others who have been looking at the data and the intermediary products that have led -- because the final peer reviews are not finished yet; they'll be published. But they've seen the data on the way.

We have asked them and others that if there are issues that you're concerned about immediately, to pull the chain on the chain, to stop it, because we want to make sure that this isn't something where we find out there's some real terrible thing that took two years for us to figure out because it's a long, lengthy process.

So we've been very clear about that, both the FDA and also to Yale, that if anybody sees things where they think there has to be immediate action, that we should be informed, but we haven't seen that yet.

Now, that doesn't necessarily mean that we're going to have a really bright or less bright

Page 271

report, but those are the kind of checks we put in place to make sure that we could be responsible in this process going forward.

So at the end of the day, we're going to carefully review the results. We are putting our trust in the systematic reviewers and in others, that they're going to come up with probably the best analysis of our results. We may have the opportunity to challenge some of those results, but the key is, it's going to be out there in public. And that's what we want to do. And then I think we'll work with the FDA to say, "Are there modifications to the label we need to make or actions we have to take if we find something that's detrimental to the public?"

MR. WALKER: That's great. Just as a quick clarification, then, you're using it as a post-market study. But in some ways, you're actually using it in a governance setting. It seems to me there's almost a decision-making, a question about decisions that you're offering up to the independent institutions.

Page 272

So I guess, why wouldn't this process have been run through the FDA as a secondary analysis, as a post-market study? I guess I'm struggling to understand why the new construct, when there's an available construct, could have been used.

DR. KUNTZ: Well, I think it depends on what the strength of the initial evidence was compared to how the FDA felt with the existing data. And it's relatively novel. I don't know. This experience might turn it into something where they write guidelines that they want to be more involved with, anything that comes up with this before.

It's not unusual for products to be challenged on the market. That happens all the time. What happened here was, it was a very large effort to challenge it, and we responded back with an independent report. And I think that -- I can't speak for the FDA at all, so I don't even want to venture for that. But my guess is that they were coupled with our process.

MS. DILLEY: David, did you have a question?

MR. DOBBINS: Just an observation. Just

Page 273

listening to the two of you, these are interesting experiences. But I don't know that they're really responsive to the IOM recommendation, because in neither case do we have research -- and, indeed, it's sort of been, a priori, stamped, it's good.

What I think is more interesting here and maybe more informative to the task is developing standards for data transparency and collection. And that leads me to a question. And I think it's a bit of follow-up to the last question.

I mean, I take it -- and I'm not trying to be unfair, so you can oppose me, but what motivated you to do this very public, high-profile, Yale-led intervention is the fact that you in some degree were put into crisis communication mode by being blindsided by a gigantic effort that's going to be reported in the New York Times.

I do think it's interesting, and what I'm interested in is what kind of model this could gather for confidence in data analysis, so less than I'm interested in what your experience is like for third-party governance, because it really isn't

Page 274

a third-party governance situation.

MS. DILLEY: That's the transparency issue.

DR. KUNTZ: Right. This was a question that we reacted to this as a response, so this was not a proactive approach. I will say, though, that I am very comfortable with the processes throughout our company. I'm a cardiologist, and the cardiology arena -- Eric's a cardiologist. I mean, we probably have more experience with structured evidence than almost every other field of medicine, and I think most people kind of recognize that.

I'm not quite sure why that is, but it's true; we have a lot of cardiac data. The company Medtronic is heavily based in cardiac outcomes, so we have very deep and, I think, responsive clinical studies in the cardiac arena.

In looking at other areas like orthopedics and others like that, where the history of evidence building is mounting but not as strong as it is in cardiology, what was a shock to me was, could it be possible that we actually have information that wasn't as clear as I'm used to in other areas.

Page 275

That was my response. And that's why we said we need to have somebody else independently review this.

I feel pretty strong about the data we have because I've looked at the data. I think it actually is pretty valid, with the FDA and everything else. But, again, if there was any chance that what I was comfortable with, in normally how we generate knowledge, might have fallen through the cracks in other areas that I wasn't comfortable, that's the main reason we went to a third party, and we'll see what they say.

MS. DILLEY: I guess a follow on to that, a question about -- and you may have mentioned this earlier when we were chatting, is the side implications of researchers, so putting data out there for the research centers and some of the complications. I mean, Eric could raise some issues around that in terms of people feeling that they can go into this area of research, and if other data are released, does that have a negative?

DR. KUNTZ: Yes. The experience I've had so

Page 276

far is that, in trying to paint the world as a transparent world, where industry who -- if you look at the breakdown of studies, it's still mainly dominant in industry, especially in the medical arena. An index people use is if you look at the last 10 years of the New England Journal of Medicine, about 50 percent of the studies published in that prestigious journal are industry sponsored. The next highest group is the VA, which is about 15 percent, then NIH, and so on.

So industry still provides a lot of the studies and, if we say, let's move to a world where industry does its regulatory requirement and makes the data publicly available, I think we can get there.

It's often complicated for academia because if you're -- and Eric will speak to this with more authority than I will. But if you're an assistant professor who's applied three times to the NIH to get a grant, it's taken you three or four years, then you have done all the hard work of getting sites on board, and writing the protocol, and doing

Page 277

the analysis, and yelling at people for not enrolling, and doing all that process for three or four years, and you got the final results, do you want to give that data up immediately? All the hard work you put into it, and have your colleagues, who didn't do anything, sit on the side and say, "I'll take that data set. Let me write the paper really quickly." That becomes a race as to who can publish, because the world of academia rewards publications.

So there is going to be, even from the academic side, a zone of protection. And maybe that zone is a year, which actually would be a good thing because it would force people to publish quicker than they are right now. But I think that there are going to be a lot of consequences of trying to push this envelope of transparency that might not be apparent up front as to who's going to be pushing back and who's not.

MS. DILLEY: Eric, are you wincing?

DR. PETERSON: No, no, no. I would actually just fully agree. I think that the other model

Page 278

that's developing similar to this NIH is even pushing a window around data that's sponsored by NIH being available then to the public as well. So I think it's a moving target of how long we'll have protection, even under our rights to publish, to try to keep our resumes look good.

I do apologize. Is there any other final questions that have to be directed my way? I've got, unfortunately, transportation outside.

MS. DILLEY: I have one question, an e-mail question, and then I know the gentleman back there had a question.

Would Duke be able, under its current structure, to take tobacco industry funds?

DR. PETERSON: I don't know, to be honest. We've never tried to do that. I guess Dr. Rose could probably speak to Duke. As a Duke investigator, you were able to do it.

MS. DILLEY: Yes?

MR. ROSE: No. I don't know of any official public policy that says to the contrary.

MS. DILLEY: A gentleman back here, and I

Page 279

don't know. Is your question to Eric?

MR. WILCOX: No. You can catch your –

(Laughter.)

MS. DILLEY: Thank you very much, by the way.

MR. WILCOX: Neil Wilcox, Lorillard Tobacco Company. It's a very interesting discussion, and I appreciate it. In response to the question about the draft guidance on MRTPs that is currently there, Dr. Parascandola said a couple times that the methods simply aren't out there yet or haven't been recognized by FDA as to what might be used to approve an MRTP.

I guess I have a statement, and then maybe somewhere in here, maybe a question.

MS. DILLEY: Excellent.

MR. WILCOX: So bear with me. I will try to not be inarticulate.

As I understand it, historically speaking, when FDA is presented a submission for product approval, they don't tell the sponsor -- albeit a drug company, a tobacco company, or academia,

Page 280

whoever may be submitting the application -- they don't tell the sponsor what methods are to be used. Instead, it's up to the sponsor to say this is my claim. This is a modified-risk product, this tobacco product. This is a modified exposure tobacco product, whatever their claim may be. Then it's up to the sponsor to say these are the methods that we're going to use to substantiate our claim.

The operative word here is claim. What is a claim for this MRTP? And then it's up to the sponsor, once again, to say these are the exposure characteristics, for instance, the portal of entry, the dose including frequency, duration, and so forth.

Then FDA would review the protocol and the results of the studies that are put forth by the sponsor and either agree or disagree that they have substantiated the product.

So with that rather lengthy introduction, my question is to Mark, under what circumstances do we expect FDA to come up with a group of methods to be used to substantiate MRTPs? And we may need David

Page 281

Ashley to weigh in here.
MS. DILLEY: You are not going to get David (inaudible – off mic.)
MR. WILCOX: I know. I'm just trying to get David involved.
DR. PARASCANDOLA: Well, I guess I would say -- again, I can't speak for FDA. I certainly didn't intend to imply that FDA hadn't recognized methods that are out there, because that's for FDA to determine what methods they're going to recognize. But I am speaking from the point of view of the science. And I think among scientists who work in this area, at least public health scientists who work independently of the tobacco industry, I don't think there is agreement on a set of methods that would sort of provide a road to approval of a modified-risk tobacco claim.
That's not to say those methods can't be developed, but I don't think there is a consensus around, say, a set of methods that could do that currently. And I think this is an area that we're continuing to support research in, and I think is a

Page 282

high priority to develop for the future.
MS. DILLEY: We have another e-mail question for you, Richard. And I think you touched on this a little bit.
"How have other devices or companies reacted to the process you've described? Do you see other companies following or will they wait to see the outcome?" I think you said, yes, they're kind of waiting, but you may have talked with your colleagues.
"Are planning to work with Yale for re-analysis, the analyses of other products."
DR. KUNTZ: I can tell you, they're on the sidelines, watching, and they're anxious. I think we've had more positive response from the drug companies. So I have done this presentation for the Institute of Medicine at a transparency workshop, where companies like Merck and GSK and others have outlined initial plans for data transparency.
Some of them are consistent with what we have. I think they are still somewhat in the

Page 283

drawing stages up front here, but they have at least announced intentions to move in that direction.
We haven't seen anybody in the device side do that yet. That doesn't necessarily mean they don't have plans to do that. I just haven't seen it. But I think what's going on is that -- I would say that, from a generic perspective, a lot of people kind of took a deep breath when they heard what we were doing. And there were some initial feedbacks saying this is the wrong thing to do up front. But I think that as time goes on, people start to see that this horse has left the barn. We're going to live in a transparent world whether we like it or not.
One way that I've always talked about it is in addition to democratizing data, which I think is really important, a smart company will realize they've got to do this anyway because data access is going to be available to anybody sooner or later.

Page 284

So because of these things, I would rather have a more formal way, where they get the right data, as opposed to trying to hack some information and say they're going to get the data some other way. So when we think about all those issues up front here, this is, I think, a reality that slowly people are kind of realizing.
MS. DILLEY: Just from the technology, what was your timeline? Do you know what the timeline is?
DR. KUNTZ: Yes. We have a mixture of a business process where people in our company get rewarded to make sure that they hit milestones mixed with an academic process, where they don't have those same incentives. And that's things like the publication process, which is totally relevant to how they do things.
So when we look at the peer-review publication process, what drives those things is how long reviewers take to review stuff, and whether they need to go back for revisions, and so on. So anyway, that process is independent, and it

Page 285

looks like we're going to get our publications out in Annals in June.

MS. DILLEY: In June? So not too long from now. Yes. Question over here, then Joanna.

MR. OGDEN: Mike Ogden with RAI Services. I think, Dr. Kuntz, this question is for you. And you partially addressed it in an answer maybe 5 or 10 minutes ago. But if I understood what you said in your presentation, you had a dozen or 14 or so studies that had all been conducted by you as the sponsor, both pre-market and post-market.

I presume, safely I'm sure, that all of those were done with full transparency to FDA. And then after the fact, so to speak, some of those conclusions were perhaps questions in terms of the risk-benefit ratio, based on a greater weight of evidence.

Imagine a world where perhaps you as the sponsor had done a half a dozen studies pre-market/post-market, and then some other studies came to light funded by, perhaps, academicians, perhaps by even your competition, that sort of now

Page 286

look like an altered risk-to-benefit ratio.

In your model with Yale, would you advocate that all of those studies be made available in the full, transparent way to fully address the issue?

DR. KUNTZ: Yes. The answer is yes. If the data -- if the other studies -- we can speak about the quality of the studies that we sponsor and contract. So we'd have to do a quality check to make sure that those other studies are out there, and there are a lot of studies that aren't done with good quality.

What I mean by poor quality is, the most common offenders of poor quality are normalization and standardization of the endpoints, the rigor of which the data was collected, and the ascertainment, which is the missing data. And missing data is always missing at bias. It's never at random.

So we put a lot of effort to make sure that we collect everything. And some studies that don't have that rigor don't collect that, and you get the wrong answer.

Page 287

So the way you talked about that scenario, the first thing would be, yes, knowledge is important to generate. If there's more data that's quality, of course we want to be able to get that data and combine it; whether people feel comfortable giving that data to us for us to combine it, or if we go to a third party so we can work it out.

But if anybody has any relevant data about our products, that's important to see it. And we've seen that with health plans. Certain health plans that have their own data have shared their data with us and also with the public. So, I mean, the idea of having competitors go after us to show that we're not there is just something we have to consider. But the answer is, if the methods are right, then we want to know what the results are. If the methods are biased, then we want to point out the bias.

MS. DILLEY: Joanna, do you have a question?

DR. COHEN: Yes. Just a question of clarification. So I think you said you haven't

Page 288

seen the results yet of the systematic review.

DR. KUNTZ: We have seen a preliminary result of the systematic review, yes.

DR. COHEN: But not the paper that's been submitted?

DR. KUNTZ: No.

DR. COHEN: Are you intending to?

DR. KUNTZ: That's a good question. We probably will. And, again, I don't want to talk about too much insider, but we have asked for maybe a few-day buffer because we're going to be hit by all the press, and we want to be able to prepare what we're going to say. So that part, I think, is going to be something that may give us an embargo, 48 hours or something, to see that.

We've also talked about whether or not -- there were some issues or ideas raised about myself writing an editorial in that journal from the perspective of what it was like for me to go through this process and the company as a whole, which would mean that I would get access to the articles, obviously, if I was going to write an

Page 289

editorial before then. But that decision has not been made, and it may not be made.

So those are the only two opportunities that we would have to be able to look at those manuscripts before they get submitted.

DR. COHEN: So I was just trying to put two and two together because you had said you hadn't seen the results, but on the other hand, the papers are going to be published in a journal. So the paper has been submitted. It's in press. Right? The systematic review is in press?

DR. KUNTZ: Yes. So just to be really clear, in the contract that we agreed with Yale was, the preliminary results of the systematic review, and actually the first drafts of the manuscripts, we would have access to, to be able to send back comments.

So what we want to do was to make sure that -- to protect the systematic reviewers, since we knew the data intimately, that if we saw some fundamental problems, we didn't want to embarrass them by having them coming back and saying, "They

Page 290

did the analysis wrong."

Now, the chances of them doing the analysis wrong is probably pretty low. But both parties agreed that we would look on the data on the preliminary. We would send our comments back. The Yale team would actually make comments on that, just so the systematic reviewers, when they wrote their final drafts and their manuscripts to be submitted to the journal, would get viewpoints from everybody. And there's no obligation they had to even read our stuff, but we gave it to them. That's the only time I actually got to see that data.

Now, the manuscripts have gone through peer review. I'm not seeing any of the peer-review responses, any of the relationships between the reviewers, and what revisions are being made. We don't get privy to that. And we haven't seen any of the revisions of the systematic reviews, which will come out as well. So our only insight was on the first round.

DR. COHEN: But they have been accepted for

Page 291

publication.

DR. KUNTZ: They were accepted before we even did the project, so the idea was that --

DR. COHEN: So that's what I'm trying to get at. So they were accepted before the work was done. I'm trying to understand that.

DR. KUNTZ: Yes. So I think what we had was an agreement. I mean, obviously, if the papers are terrible, the publisher is not going to -- the editor is not going to put it out there. But the idea was that we had worked with -- and, again, I give all credit to Christine Laine at the Annals and others to say that this is a novel approach about the data transparency process and so on. And we wanted to make sure that we could come out in a systematic way to explain this story that made sense.

What we thought would be good is to have both publications from these different groups come out in a prestigious tier-one journal. And our first choice was to talk to Annals. And when we told them about this process, they said, "Yes, we

Page 292

would be happy to do that," just like other journals may negotiate. They would be the primary group that would publish this.

Now, I guess what I don't know is, if the reviewers feel like the quality of the work isn't worthy of publication, well, then they don't publish it. But my guess is, with these two standing systematic reviewers, that's not going to be an issue about the quality of the stuff, especially if they follow the peer-review process.

So this is more about -- and I think also with that idea was not only were the results of the study going to be important for Annals, but also the editorials that would surround that, comments about data transparency, the journey, and all that kind of stuff was I think what they are going to try to focus that issue on.

MS. DILLEY: So that's the study -- it's the analysis itself, but it's also the fact that this is a new model.

DR. KUNTZ: Yes. And, again, I don't want to speak for the Annals because I'm two or three

Page 293

degrees removed on this process. But it's been a very positive relationship by them at least trying to help push this journey further. In all the comments I made about what they did, the details might be wrong, but that's my understanding.

MS. DILLEY: So yes, Mark?

DR. PARASCANDOLA: I just wanted to ask a follow-up question, too, because I think this is a great example. So when you talk about the data being made available, obviously it was made to those who are doing the analysis. But I thought you had referred also to data being made more publicly available once it's been de-identified, so I guess I was curious how that process works.

DR. KUNTZ: So we have committed to making the data publicly available. We haven't committed on the methodology yet. And that's still a process ongoing. And we're trying to time it for the announcement of the process, when the publications come out. So we're actually in the throes of trying to understand this process.

I think we all agreed that the first

Page 294

time -- industry has never done this. There's never been, in the history of drugs or devices in biologics, anyone who's made patient-level data available to the public. And there is a lot of concerns about this process. So we want to make sure that we move in a measured pace and understand that process.

So I can tell you, it won't be a spreadsheet put on the Web that people can get with every piece of data. We will have a process which is very fair. It will be completely controlled by Yale. It won't be controlled by Medtronic. And it will be done with the best intentions by those individuals I talked about on the steering committee, and others, to make sure that responsible questions are being asked and responsible research is being done, regardless of whether it means anything good or bad for Medtronic.

We talk a lot about industry's bad views and not reporting adverse events. We actually make products that actually help patients, too, as well.

Page 295

And so patients depend on having these products out there. And when we pull products off the market, we get a lot of input from patients that say, "We needed that product. You're pulling away from the market. Why is that?" So we also want to assure that any benefits of the products we make for patients who can get there also don't get thwarted by irresponsible analysis.

So it's a big burden for us, for responsibility, to figure out how to navigate through this, to be both publicly responsible, but also not go too overboard that we end up with a situation that might harm people because of lack of access to a product that might be helpful to them as well.

Again, this is, I think, something that's fully understood by these independent groups that are working with us. And they are trying to work through that process. And there's no formula. There's no roadmap for this.

MS. DILLEY: We have time for maybe one or two more questions, if there are any. We weren't

Page 296

going to keep you up here a whole other hour, Richard. Don't worry. Mark.

So any more? Any online? One more.

MR. DILLARD: Jim Dillard, Altria Client Services. Richard, you just brought up something really interesting that I hadn't thought about until you started talk about it. But the public availability of data that the public has never had available to it at this point, can you talk a little bit about what were some of the areas that you were thinking about as you went through some of those lists and kind of came up with the questions? What were some of the thoughts Medtronic was having about what could some of the downsides be about having this data publicly available, where anybody could access it?

I only bring that up -- and I'm not trying to bring up a whole other topic, but we're sort of faced with that in the tobacco industry, which is we're getting ready to publish harmful and potentially harmful constituent data for the public. And so it would be a good sort of

Page 297

conversation and a parallel to just hear from you, what are the struggles that you've thought of.

DR. KUNTZ: Our biggest concern are litigant firms. And we know that there's a profit by litigant firms to try to take data and view it in a view that would be their business model for making profit, and we've seen that happen in the past.

So when we look at the fact that biostatistical standards are evolving, the statistical -- let me give you an example. I can tell you that the systematic reviews are not completely harmonized. These are two outstanding groups that did reviews of all this stuff, and they have slightly different conclusions, at least the first draft I saw.

So we know that methodologies, even in the best intent by the most talented individuals, often won't be fully coherent on that level. So if you look at the next level spectrum, which is nefarious manipulation, that data up front, that's the biggest downside by far.

We don't fear good methodology finding

Page 298

problems in our products. We want to know that just as well as anybody does. We don't fear the universities working with us and the FDA and other people getting access to it. We fear individuals who have a business model to make money by potentially using data that they can manipulate. That's the biggest concern.

One could say, "Well, as long as they make their methods transparent, we can be able to challenge them." In our field, the first two or three sentences of a result are all you get to listen to. It's often you don't get into the methods all the time, especially when it becomes a headline on a paper. And we know the thresholds that get into media often aren't reviewed by statistical editors at certain media outlets.

So these are the biggest concerns we have, and these are shared by all of the other perspectives I think up front here because of this. And I don't want to taint litigant firms. They serve people, no question, that there are individuals who need to be protected to fight

Page 299

against -- who don't have the capabilities, and that's all good. But we've seen behavior that might not be consistent with trying to find the truth all the time, and that's our biggest concern.

MS. DILLEY: I just want to thank you, Mark, and Eric, who's not here any longer, for your comments and also taking questions and answers, so thank you.

(Applause.)

Adjournment

MS DILLEY: We're going to conclude today's session. I just wanted to give you a sense of tomorrow.

On your agenda, we start at 8:30 in the morning, and we'll go over some of the details of how the day is going to go. Then we have the public comment period from 9:00 to 9:30. And then we'll start the next panel in Challenges in Conducting Industry-Sponsored Research with another set of panelists.

We have two before a break and then, again, I just want to remind people that that break is

Page 300

15 minutes, not 45 minutes. So we'll start back up at 10:15, and then go to 11:45, where we'll switch gears to Q&A, and some concluding comments, and close the session at 1:00, no later than 1:00.

So have a good evening and we'll see you tomorrow.

(Whereupon, at 3:56 p.m., the meeting was adjourned.)

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